UNIVERSITAT ROVIRA I VIRGILI

THE ACTIVATION OF DIBORON REAGENTS AND THEIR APPLICATION IN CATALYTIC BORON ADDITIONS TO ALKENES

Amadeu Bonet Laplana

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Amadeu Bonet Laplana
Doctoral Thesis

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“The activation of diboron reagents and their application in catalytic boron addition to alkenes”

DOCTORAL THESIS

Supervised by

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Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

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FAIG CONSTAR:

Que el present treball, titulat “The activation of diboron reagents and their application in catalytic boron addition to alkenes”, que presenta en Amadeu Bonet Laplana per a l´obtenció del títol de Doctor, ha estat realitzat sota la meva direcció i la co-direcció del Dr. Henrik Gulyás, del Departament de Química Fìsica i Química Inorgànica de la Universitat Rovira i Virgili.

Tarragona, 2 de marc del 2012

Dra. Maria Elena Fernández Dr. Henrik Gulyás

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Agraïments

He deixat això per al final perquè sóc conscient del complicat que serà poder agrair i expressar en unes pàgines 4 anys d'una vida. Quan aquest camí va començar, era una època de canvis constants en la meva vida i aquell novembre no va ser una excepció. Un cop em vaig traure del cap fer la tesi a orgànica vaig trucar a la porta de l'Elena, no era la primera vegada que en parlàvem, però aquesta vegada seria diferent. Anava a demanar-li que si l'oferta per a fer la tesis amb ella seguia en peu, la faria. A dia d'avui i vist amb la perspectiva del temps, dels camins que he pres i on m'han portat no hi ha cosa que agraeixi més que aquell novembre.

Vull començar agrair-li a l'Elena, responsable de tot el que científicament sóc. Perquè al principi va confiar en mi, perquè encara que jo no ho creia va apostar per mi en el moment que ho havia de fer, hem va donar llibertat per experimentar quan ho necessitava i per donar-me ales ara que vull volar. Ets una persona la qual admiro, perquè ets un exemple increïble de que es pot arribar a portar una família (nombrosa) i una carrera d'èxit i fer-ho amb alegria! Espero haver-me impregnat prou de l'aura que t'acompanya per a aconseguir algun dia acostar-me a el que has aconseguit. Treballar amb bor ha estat exquisit, per la química, pels resultats, pels congressos, per la gent que he conegut, per 4 anys de bons records que m'emporto amb mi. També t'he d'agrair donar-me l' oportunitat de canviar la visió de la catàlisis. En el moment en què vaig començar, veia la catàlisis com una disciplina més irracional, llunyana i menys consistent que la química orgànica; però que equivocat estava! Com no podia veure que les dos tenien tant en comú? Si al final amb la catàlisis he acabat fent el que volia, i al damunt no he necessitat metall! :D

Encara que va arribar uns anys mes tard vull agrair al Henrik tot el que m'ha ensenyat. Vam començar jugant a bàsquet els dijous (sempre has estat un rival duríssim, serà pel físic xD) i has acabat sent el meu co-director de tesis. El grup va millorar algunes coses en la manera de fer amb la teva arribada. Tu m'has donat una visió encara més crítica i diferent de la química la qual agraeixo moltíssim.

Quan vaig entrar al laboratori, ni el nostre petit grup del bor era tan gran (érem 2 o 3) ni estàvem tots tan units com ara. La veritat és que en aquells temps, el labo en general estava bastant dividit entre veterans que estaven en guerres de guerrilles o que anaven bastant a la seva i joves que acabàvem d'entrar i volíem canviar el món i fer un labo millor i més just per a tots. La primera persona que hem va supervisar al labo va ser el Jesús. Ell ja era doctor, ja estava buscant feina, i va ser ell qui hem va ensenyar al principi com funcionava tot. Jo l'admiro molt perquè a part de ser un gran científic va ser ell qui em va ensenyar, de qui vaig aprendre al principi i qui em va donar un dels consells que més em van marcar en la meva vida.

En aquell labo tenia, tinc i tindre un gran amic que es quedarà almenys fins l'octubre. Ell és el responsable més gran de què a dia d'avui estigui aquí perquè gràcies a ell vaig acabar triant química. Javier Mazuela, després de gairebé 10 anys fen un mateix camí tocarà (a no se que passi alguna cosa molt estranya a última hora) separar-nos. No saps com he agraït durant aquests anys totes les coses que hem fet, estant al meu costat en els bons i en els mals moments, i no tens ni idea de com et trobaré a faltar en el meu dia a dia. Coneixent-te se que no perdrem el contacte i que sempre podré comptar amb tu (i viceversa) i a més, qui sap si dintre d'uns anys tornem a estar junts jeje

En aquell mateix labo també hi havia una persona que sempre he apreciat moltíssim i que em va ajudar molt al principi. L'Eva Raluy, per alguns la *comanche*, per a altres la *leyenda del corcho*, per a altres la *celestina*. Vam compartir les últimes pràctiques que feia com a estudiant de carrera i les primeres pràctiques que feia ara vigilant com a associat (vigilant als de la meva promoció :facepalm:). Durant aquella època vam sortir molt i vam riure moltíssim. Se que sempre podem comptar amb tu. Espero que els camins no es separin gaire més.

Però en aquell labo vaig conèixer molta més gent, amb la que hem compartit moltes coses. En la vitrina del vents estava la Vero, una de les persones que més puc admirà, és segurament, la persona més forta, amb força de voluntat, més compromesa i lluitadora que conec, a part de ser un coco. Va ser una de les primeres persones amb les quals vaig congeniar i enseguida es va convertir en un ritual anar a fer petar la xerrada mentre ella estava fent columna asseguda. Moltes gràcies Vero per fer-me part de la teva vida i compartir tantes i tantes coses. T'esperem a Bristol, que ja saps que allà passes com a nativa (a part de l'angles xD)

Abans de seguir avançant, aquí he de parlar de l'Ali. Possiblement la millor persona, més intel·ligent i segurament més infravalorada que conec. Abans de tenir una beca, vaig tenir un associat i gràcies a aquest vam poder compartir moltes i moltes classes i pràctiques. Vull agrair-te tot el suport del principi, tots els riures del labo, tant a pràctiques com al nostre, i de fora. Per totes les converses i ensenyar-me tantes coses de la vida. L' oportunitat que ens vas donar de conèixer casa teva i la possibilitat de tenir un amic amb un cor tan gran com tu. Espero veure't aviat.

Al cap de poc temps ja va arribar la primera de les cristinetes, l'alegria del labo mentre no esta fent càlculs o no esta massa estressada (llavors podríem dir que mai? xD). Sempre amb un somriure, sempre amb una rialla, sempre amb un acudit que a mi sí que em feien gràcia. La veritat és que ens ho vam passar bastant bé en l'època dels dissabtes i Batea va ser genial. Moltes gràcies per les correccions ortogràfiques i per intentar que destrossi una mica menys el català. Espero que no perdem el contacte i almenys continuïs amb la costum d'anar contestant els mails de tant en tant.

I amb la arribada de la Cristina Pubill-Ulldemolins, també va arribar l'Oriol (quina manera de lligar-ho no? xD). Dintre d'aquella aparença de passota es troba un dels millors amics que un pot tenir, i encara una millor persona. Gràcies per compartir tantes coses i estar al meu costat quan ho he necessitat. La veritat és que hem rigut molt tant al labo con fora d'ell. Me n' alegro molt d'haver tingut l'oportunitat de coneixe't i sé que m'emporto un amic per sempre. Sé que encara que estiguem lluny no perdrem el contacte i pensa que no em perdré per a res el dia de la teva presentació de tesis (sempre que compleixis lo que t'has proposat jeje)

Amb aquesta anyada de Màster i encara que ja feia un temps que estava al grup també hi ha la Mercè. La mama del grup, gràcies Mercè per sempre tenir un bon consell o unes paraules d'ànim i per en definitiva fer-nos a tots els teus *fills* la vida més fàcil. Ser que moltes vegades t'has d'haver sentit rodejada de nens inconscients, però i lo bé que ens ho hem passat?

D'aquella anyada també es una de les persones més increïble que conec. Manu segurament no ets conscient de com et tinc, vas entrar en el nostre grup amb l'humilitat d'un aprenent sent el més expert dels veterans en aquest camí que és la vida. Doctorat i feina, tot alhora i al damunt amb família, a mi que ja em costa està pendent de les quatre coses que em rodegen i tu vas carregar amb tot (evidentment Marie-Anne té molta culpa jeje). Els 3 anys de doctorat van donar peu a tres fills, sort que vas acabar ja!!! Jeje Gràcies Manu per sempre poder parlar, per les xerrades filosòfiques de la vida mentrestant carregaves i descarregaves el reactor. Ets un exemple a seguir. Me n'alegro molt d'haver-te conegut tant a tu com a la teva dona i espero que per molt lluny que estigui puguem continuar amb contacte

Com sempre passa no érem prous, i sense haver fet reformes per aconseguir un segon pis al seminari ja va entrar sang nova.

Jessi, Eli; Eli Jessi, inseparables fins al doctorat. Primer va entrar la "personaje" (en aquell moment encara Pebels i passant per 20 mil noms diferents), i amb ella un munt de coses, un munt d'històries. Gràcies per ser un tros de pa i una amiga. Saps que per molt que t'emprenyem sempre és amb *carinyo*. Gràcies per tot el que hem rigut (amb tu i de tu xD) i per totes les coses que encara ens queden per riure. Sé que tant amb tu com amb el tronista, sous dos grans persones en les que podem contar sempre. No sé si baixarem molt o poc de Bristol però bitllets per a la primera setmana de febrer sempre tindrem jeje

Eli, senyora més gran que jo :P El camí segur que es veu llarg, però et ben juro jo que quan estàs escrivint aquestes línies et dones compte que això ha passat molt ràpid. Tens la sort que, com jo, el tens a prop. A mi hem van dir que això té un valor incalculable i ara t'ho dic a tu. Gràcies per tenir aquesta riallada inconfusible d'orella a orella des del dilluns al mati fins al diumenge a la nit.

Al grup també va anar entrant gent i nosaltres vam duplicar Cristina i Jessica. Cris ets una treballadora incansable, com la que et va ensenyar, però amb un coco que no tenen altres. Gràcies per ser una alegria i parlar amb un volum tan alt, així tots podem xafardejar del que dius jeje Merci per a intentar sempre arrencar un somriure a tothom. Cada dia lluites amb tu mateixa, i aquest esperit és el que et farà arribar molt lluny.

Ai Jessica, he estat molt unit a tu l' última part del meu doctorat. Ets una persona genial que gràcies a que l'Elena ens va portant de congrés en congrés he tingut l'oportunitat de descobrir. Quines excursions per Edimburg no? jeje Ets una persona treballadora, lleial, simpàtica, intel·ligent i sobretot una amiga la qual aprecio moltíssim. Encara que no t'ho creguis has estat un enorme suport aquest últim tram. Hem rigut molt i espero que continuem rient junts durant molt de temps.

Fa també relativament poc tenim la Raquel entre nosaltres, gràcies per tenir tanta i tanta paciència amb nosaltres. Que tenies paciència ja ho sabia d'aquell estiu a Bayer, però tanta? Merci per sempre tenir un moment per a xerrar i per a riure. Molta sort en l'examen, tots estem amb tu i a diferència nostra sabem que tu aquí t'hi passaràs molt anys.

A la Sabi, que encara que de vegades sembla que no hi ets, sempre estàs present. A tots els que durant aquest període també ha passat, gent inoblidable que sempre et quedes amb moltes coses d'ells: el sempre recordat Aitor (*Gipa, the legend*), Caro, la petita *peleona*, l'Ariadna, l'alegria dels supercrítics i les heterogènies Isabel, Dolores i Tati. Sobretot la Dolores amb la que he compartit tota la carrera i encara que durant el doctorat estàvem a diferents labos i fent diferent química sempre ha estat una persona fantàstica amb la que podies parlar sempre de tot. A tots us desitjo el millor, estigueu on estigueu i espero trobar-vos en el camí ben aviat.

Vull agrair al Cyril per sempre estar disposat a ajudar-me, al Bernaber per sempre tenir un moment per a una pregunta, per a una conversa o un consell i a tots els professors, a Jorge per sempre mostrar interès, a l'Anna Maria Masdeu per confiar en mi quan era un marrec recent sortit de la carrera i donar-me el primer associat. A Carmen i Sergio pels sopars i per tenir sempre la predisposició de parlar del que sigui. A Òscar i Montse per totes les pràctiques que hem compartit i per estar sempre disposats a donar un cop de mà. A l'Aurora per tenir sempre una paraula d'ànim durant el camí i en conjunt a tots els professors del departament. A Yolanda i Pilar, per tenir-me sempre confiança i respondre sempre amb un somriure. A l'Arantxa, que durant aquest camí ens va deixar abans d'hora, tots et tenim molt present. Espero que des d'allà dalt estiguis contenta de tot el que passa aquí baix.

Als nous, els que comenceu i veieu això que estic escrivint com una cosa tan llunyana, tranquils que ni tan sols us en donareu conte i us estarà fent tan de mal el braç d'escriure com a mi. Marc, Gerard, Laia, Jessica (III) i Xavi, sou un grup fantàstic i hem sento orgullós de veure que hi ha tan bon rollo. Això es un petit tresor que heu d'intentar conservar. Fer la tesi amb amics té un valor incalculable, hi haurà moments de cert egoisme, d'estrès, pressió però si esteu units no hi haurà res que una cervesa (o un gintònic no Marc?) en un sopar no pugui arreglar. Us desitjo tots els èxits del món, tranquils que ens anirem veient.

I dels nous, als que els nous no podeu conèixer. Marta i Yvette, gràcies per passar amb el Javi i amb mi aquell congres de puta mare a Estocolm. A la Clara i a la Bianca, per tenir cada cop que es passen per la Uni un somriure i a la Vanessa, perquè m'has ensenyat molt.

A la Maria Jose, al Jordi, el Ramon i la Rosa, sense ells 4 aquesta tesis i totes les demes no haurien estat possibles. De tots me'n duc un bon record. Especialment de la Rosa, capaç de venir un dissabte i fer proves boges ajuntant dos columnes quirals per a intentar separar un pic no ho fa qualsevol ;)

També vull agrair a la Cathy Crudden per donar-me l'oportunitat d'anar al seu laboratori quan era encara un marrec i sobretot a la Jenny Du, al Steve, el Ben, el Jhon, al Daisuke i sobretot al Ahmad per fer de la meva aventura americana un record divertit ple d'historietes.

A tots els que han passat per aquí d'estància, però sobretot vull destacar a dos parelles. A l'Oli i al Nico, els dos francesos que he tingut el plaer de fer moltes i moltes coses. Amics per jugar a paddle, per veure i demanar consell. Tenir postdocs amics és un pou de saviesa que vaig intentar aprofitar. Sou collonuts i espero que estiguem sempre en contacte. A l'Amo i al Graham, hem tingut la sort de tenir-los els dos al grup i la sort de poder compartir moltes coses amb ells. Persones divertides i excepcionals, espero tornar a coincidir amb vosaltres en un futur pròxim.

Als amics de fora d'aquí, sobretot al Toni, l'Aida i l'Isa Castro tres persones excepcionals que estimo molt i que durant aquesta època han estat més pendents de mi que jo d'ells. Tranquils, tot s'acaba, la festa tornarà a començar.

A la meva família, diversificada, estranya i complicada. Des de ma mare, fins a mon pare i l'Anna passant per tots els meus germans (David, Inés, Helena i Vika), cosins i tiets, passant per l'Amadeu i la Cori i les meves avies, perquè és gràcies a ells i totes les coses que he viscut amb ells que sóc qui sóc i no un altre. Als meus petits gatets, a Cali i Ganxet, que tanta companyia fan quan un passa hores i nits escrivint.

Sobretot vull agrair a mon pare, qui en aquests 4 anys ha estat confiant amb mi i recolzant-me com ningú. És una persona excepcional, treballadora, lluitadora com cap que conec i que mai es dona per vençuda. Des del seu màster de la vida, m'ha ensenyat coses que un no aprèn a la universitat. M'ha ensenyat a treure forces d'on no n'hi ha, a què un sempre s'ha d'aixecar i mirar al davant, a què un sempre ha de tenir un objectiu clar i lluitar per ell i per ensenyar-me que un no s'ha de perdre dintre de les petites batalletes del bosc sinó que s'ha de pujar a l'altiplà per així veure la immensitat de l'horitzó i comprovar que aquelles batalletes del bosc no eren lo important. Espero haver-me impregnat de mil coses de tu.

A l'Amadeu Cortés, pare 2 durant molt de temps, i que encara que passin els anys encara es preocupa per mi. Segurament una de les persones amb el cor més gran que conec i amb sempre ganes de creixement personal. Tu i la Cori m'heu ajudat moltíssim durant aquests anys, sé que no han estat fàcils i ningú diu que els pròxims 4 hagin de ser millors però espero un dia poder-vos tornar tot el que m'heu donat i espero un dia poder ser tan bona persona com ho sou vosaltres.

A la Judit, a la meva cosineta, perquè feia temps que no redescobríem la nit. Les rialles i els mojitos, per lo bé que t'has portat amb nosaltres des del minut 0, per tot el que ha significat i significarà Mallorca. T'esprem a UK, encara que no faci el mateix temps segur que trobem algun lloc per sortir de marxa.

Al David, perquè desprès d'uns temps foscos tornem a ser tan terribles com abans, tot i que ara amb una mica més de seny però amb la mateixa rauxa que abans. Gràcies per estar atent i per totes les coses que hem fet i totes les coses amb les que m'has fet riure. Encara que no t'ho creguis m'has ajudat més del que et puguis pensar.

A l'Helena, perquè un dia llegiràs aquestes línies te'n recordaràs que vam intentar fer una tapa. Perquè encara et quedi molt lluny, continuïs estudiant i un dia pugis escriure un treball tan llarg tan llarg, que hagis d'agrair a tanta gent com jo jeje. Continua sent la que ets, només els que s'esforcen molt per el que volen ho aconsegueixen.

A mon àvia, que no està massa d'acord que vagi a Anglaterra i que ho ha intentat de totes totes que no ho faci. M'ha ajudat molt en moments molt complicats i tenir una persona així al costat és molt important per a mi.

I per últim i tots comprendreu que no menys important a tu Angie. Ets el sentit de tots els camins que he pres i les conseqüències que han tingut. Qui havia de dir que aquells dos que només es picaven acabarien així? Tot va començar en festes, amb quedar-se una estona al labo sense tenir massa motiu, amb veure gots d'aigua de mitja hora, amb el nitrogen, amb el Twister i caiphirinyes, amb la bicicleta elèctrica. Tants i tants records, tants i tants moments. Ets la persona més important de la meva vida, i sense cap tipus de dubte, sense el teu ajut i suport aquesta tesis i tantes altres coses d'aquest últims anys no haurien estat possibles. Gràcies per tantes imatges, tantes fotografies, tants aromes i moments feliços que es queden gravats a la ment amb ferro roent, gràcies per voler continuar aquesta aventura amb mi, espero que aquest viatge duri molts i molts anys. T'estimo.

"Tall oaks from little acorns grow."

David Everett *quoted by* ***H. C. Brown****, Nobel Lecture 1979*

Chapter 1: General introduction and objectives

Chapter 2: (NHC)Copper mediated β-boration of activated olefins

Chapter 3: Palladium and Iron mediated β-boration reaction

Chapter 4: Organocatalytic β-boration of α,β-unsaturated carbonyl compounds

Chapter 5: Organocatalytic diboration and its enantioselective approach

Never walk on the traveled path because it
only leads where others have been.

Graham Bell

1 General Introduction and Objectives

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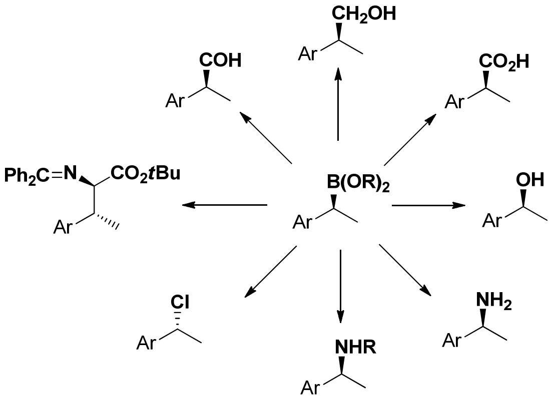
1.1 General overview

Borane compounds are considered one of the most important class of compounds because they can be utilized as functional molecules,[1] functional polymers,[2] ^{10}B carriers for neutron capture therapy,[3] biologically active compounds,[4] and are probably one of the most versatile intermediates in organic synthesis since the C-B bond can be transformed in to new C-O, C-N and C-C bonds (Scheme 1.1).[5]

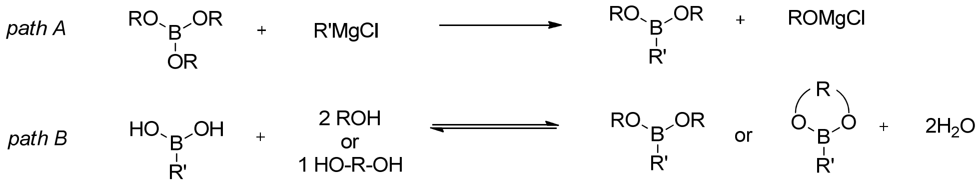


Scheme 1.1: Examples of transformations of C-B bond

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

a) The superior stability of organoboronic esters to the air, water and silica gel chromatography. This is related to the partial donation of the lone pair of electrons of the oxygen atoms into the empty *p*-orbital of the boron. However, the degree of stability depends on the nature of the organoboronic ester. Thus, bulky, aliphatic and cyclic organoboronic ester compounds are, in general, easy to purify, to store and to handle. Alternatively, unhindered, aromatic and acyclic derivatives are less robust and in some cases can be sensitive to air, water and acidic media such as silica gel.[6]

b) Secondly, we can find a large scope of organoboronic esters readily commercially available or easy to synthesize. There are two general synthetic routes towards the synthesis of organoboronic esters. The first one (Scheme 1.2, *path A*) is the transmetallation of the corresponding trialkoxiborane with organolithium or organomagnesium compound. The second one (Scheme 1.2, *path B*) is the esterification of organoboronic acid with the corresponding alcohol.



Scheme 1.2: General synthesis of organoboronic esters

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

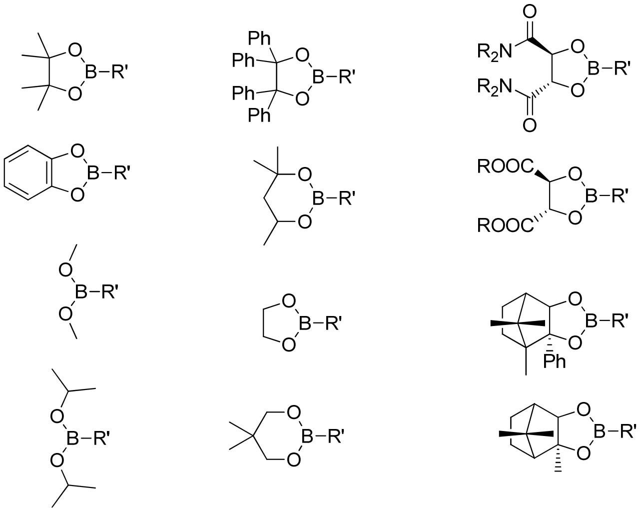


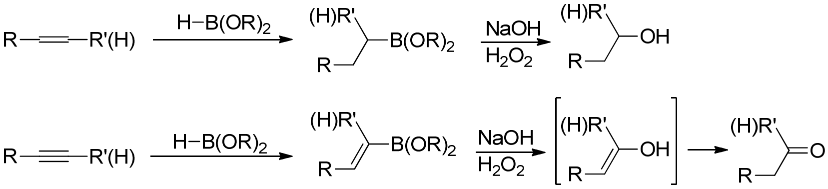
Figure 1.1: Palette of organoboronic esters

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

Taking into consideration the last point, the addition of borane reagent to C=C or C≡C can be divided into two main groups depending on the nature of the borane reagent: hydroboranes and diboranes.

1.2 Hydroboranes: Reagents and general overview of the hydroboration reaction

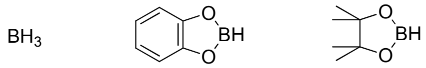
Hydroboranes are the preferred reagents to introduce one boryl moiety to an unsaturated molecule, through a hydroboration reaction. In this reaction, the hydride and boryl group are added in a *syn* fashion. In general, the hydroboration reaction provides the organoborane compound with the boryl group attached to the less-substituted carbon. Hydroboration of alkenes and alkynes provide a convenient synthetic route towards alcohols, ketones and aldehydes, when oxidation of C-B with H_2O_2/NaOH is involved in the work up (Scheme 1.3).



Scheme 1.3: General scheme of hydroboration of alkenes and alkynes and subsequent oxidation towards the synthesis of alcohols, ketones and aldehydes

Hydroboration was originally performed as a non-catalyzed reaction. The reaction was first reported by H.C. Brown and coworkers in the late 1950s[7] and was recognized with the Nobel Prize in Chemistry in 1979.[8] He used sodium borohydride ($NaBH_4$) for the hydroboration of cyclic olefins.[9] BH_3 (**1.1**) reacted with triple bonds providing a mixture of alkenylboranes and alkyldiboranes, due to the high reactivity of borane.[7] In order to increase the selectivity of the reaction, dialkoxiborane reagents were used as an alternative.

Catecholborane (**1.2**) and pinacolborane (**1.3**) are among the most commonly used dialkoxiborane reagents (Figure 1.2), both can easily be prepared by the reaction of borane (**1.1**) and the corresponding dialcohol. Catecholborane is more Lewis acidic, more reactive and more sensitive to hydrolysis than pinacolborane due to the positive resonance effect of the phenolic oxygens towards the benzene ring that minimizes the π donation from the oxygen atom to the boron atom.



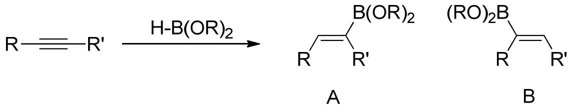
1.1 **1.2** **1.3**

Figure 1.2: Most common borane reagents: Borane (**1.1**), Catecholborane (**1.2**) and Pinacolborane (**1.3**)

Catecholborane can react without any catalyst with alkynes at high temperatures (70ºC-100ºC) giving the corresponding alkenylboronate ester.[10] However, catecholborane has other intrinsic unsolved problems because catecholborane often decompose in catalytic conditions, which means that an excess of catecholborane needs to be used. Also, catecholborane is a reducing agent.[11] Another disadvantage is the high sensitivity of the organoborane compounds that contains the catecholboryl unit, towards purification with silica-gel flash cromatography.

A very convenient alternative is the pinacolborane reagent because it is more stable (less Lewis acidic than catecholborane).[12] Pinacolborane can be added to alkynes and alkenes under mild conditions, in some cases with better chemoselectivity than catecholborane (Table 1.1) and also has the advantage that the products can be purified by cromatography.

Table 1.1: Selectivities in catecholborane and pinacolborane addition to alkynes

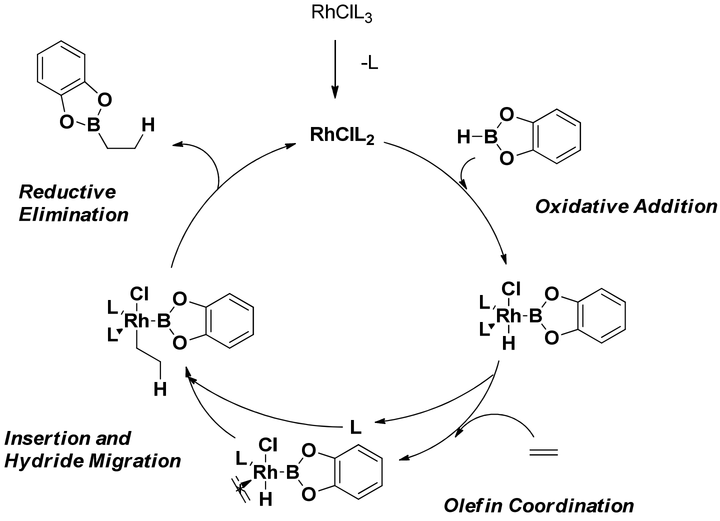


	Hybroboronate	**A:B**
R=Pr, R'=Me	Pinacolborane	93:7
	Catecholborane	60:40
R=Ph, R'=Me	Pinacolborane	85:15
	Catecholborane	73:27

The non-catalyzed hydroboration reaction has a series of limitations in terms of chemoselectivity and substrate scope, for that reason the activation of dialkoxiboranes with transition metal complexes opened new doors towards their application in synthetic organic chemistry.

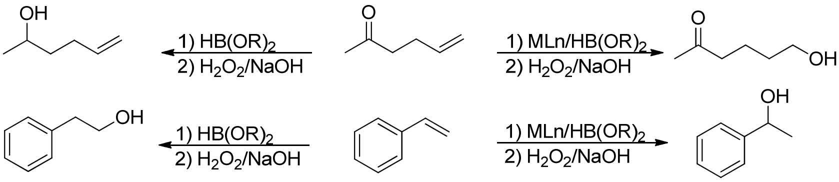
Kono and coworkers demonstrated that catecholborane could be oxidatively added to Rh(I) in the Wilkinson catalyst [RhCl(PPh$_3$)$_3$], resulting in the formation of the Rh(III) complex [RhClH(Bcat)(PPh$_3$)$_3$]. [13]

Mannig and Nöth were the first to demonstrate that the Wilkinson catalyst could catalyze the hydroboration of olefins with catecholborane.[14] These authors and others suggested a catalytic cycle for the rhodium-mediated hydroboration reaction of alkenes (Scheme 1.4).[15,16,17] The cycle could starts with the decoordination of one ligand from [RhClL$_3$] towards the oxidative addition of the dialkoxiborane reagent. The next step is the olefin coordination to the metallic center, followed by 1,2-insertion. The last step is the reductive elimination that gives the desired product.



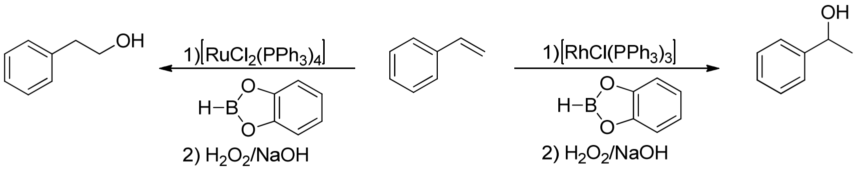
Scheme 1.4: Catalytic cycle of hydroboration reaction catalyzed by Wilkinson catalyst

However, despite the plausible mechanism suggested, there are many other aspects that are still controversial, such as the order of insertion of the olefin followed by hydride migration versus boryl migration. Theoretical studies in this field have also made a considerable contribution to the understanding, and helped to clarify the mechanism in each case.[18] But the most interesting is that the transition metal catalyzed hydroboration has shown a different reactivity, providing different chemo-, regio- and stereoselectivity, with respect to uncatalyzed hydroboration reactions (Scheme 1.5).



Scheme 1.5: Chemo-, regio-, and stereoselectivity in catalyzed and uncatalyzed hydroboration/oxidation of olefins

The nature of the metal, ligand, reaction conditions, substrate and hydroborane reagent also influenced the activity and the selectivity of the reaction (Scheme 1.6).[19]



Scheme 1.6: Influence of the nature of the catalytic system on the regioselectivity of the hydroboration/oxidation reaction of styrene

Unfortunately, the reason for the preference for the branched or linear products in rhodium mediated hydroboration has not yet been well understood. Hayashi and coworkers[20] suggested that in the case of vinylarenes as substrate, the branched hydroborated product can be favored by the stabilization of η^3-benzylrhodium complexes (Figure 1.3).

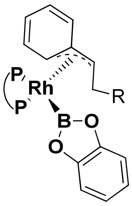
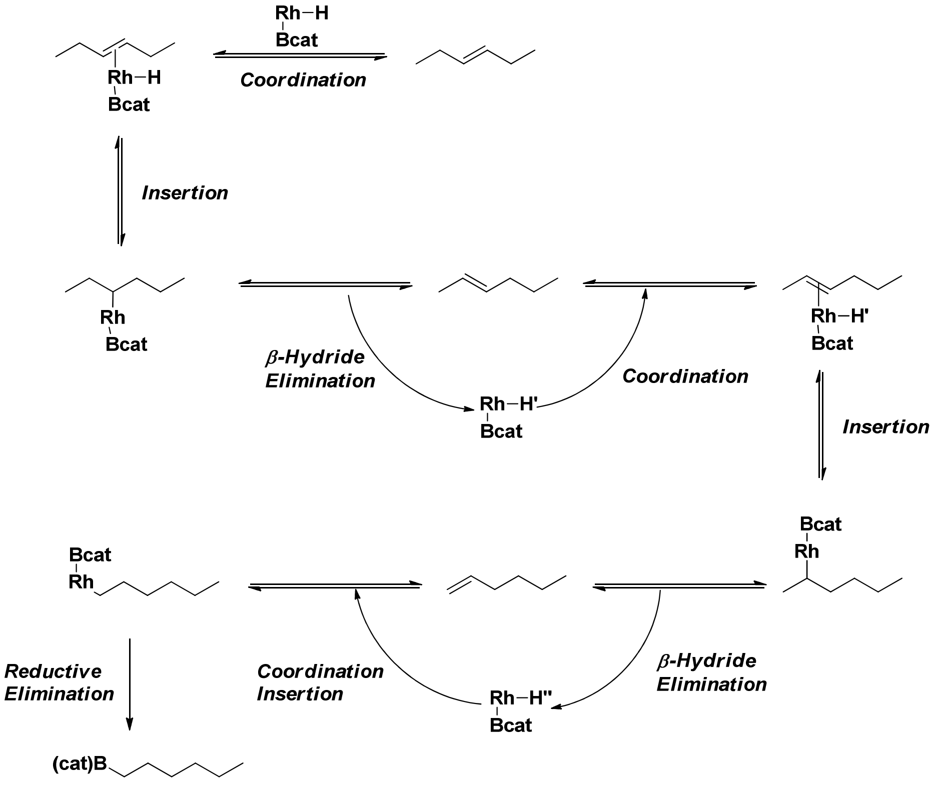


Figure 1.3: Suggested key intermediate in hydroboration of vinylarenes

The directing effect of electronegative substituents on perfluoroalkylethylenes also favors the regioselective Rh-mediated hydroboration towards the branched isomer.[21] However, in the rhodium catalyzed hydroboration of internal olefins there is an intrinsic isomerization (chain walking) of the double bond towards the terminal position of aliphatic alkenes, and the hydroborated product is predominantly the linear isomer (Scheme 1.7).[22]

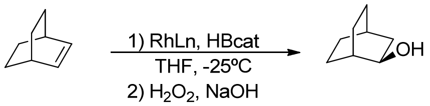


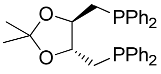
Scheme 1.7: Hydroboration reaction of internal olefins mediated with rhodium complexes

The use of transition metal catalysts modified with chiral ligands opened the possibility to induce enantioselectivity in the hydroboration reaction. In 1988, the first catalytic asymmetric hydroboration of olefins was reported by Burgess and coworkers[23] for substrates such as norbornene in the presence of a Rh catalyst modified with the chiral diphosphine [(−)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] (R,R)-Diop (**1.4**) (Table 1.2, entry 1). Burguess and coworkers improved the asymmetric induction in the hydroboration of norbornene using analogous reaction conditions but changing the bidentate chiral diphosphine ligand to [(2S,4S)-2,4-Bis(diphenylphosphino)pentane] (S,S)-BDPP (**1.5**) and [(−)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis((1-

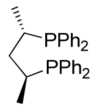
anisole)phenylphosphino)butane] 2-(R,R)-MeODiop (**1.6**) (Table 1.2, entries 2 and 3).

Table 1.2: Enantioselective hydroboration of norbornene.

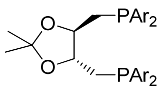




1.4



1.5



Ar= 2-MeO-C_6H_4

1.6

Entry	Catalytic system	Yield (%)	Ee (%)
1	[Rh(μ-Cl(COD)$_2$]/(R,R)-(-)Diop (**1.4**)	99	57
2	[Rh(μ-Cl(COD)$_2$]/(S,S)-BDPP (**1.5**)	95	80
3	[Rh(μ-Cl(COD)$_2$]/2-(R,R)-MeODiop (**1.6**)	95	82

However, the best enantiomeric excesses were observed with rhodium complexes modified with atropoisomeric chiral ligands.[24] [(R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] (R)-BINAP (**1.7**) is one of the best ligands for rhodium mediated hydroboration of styrenes, in terms of asymmetric induction and activity,[20] but it needs very low temperatures to guarantee high enantioselectivities (Figure 1.4).

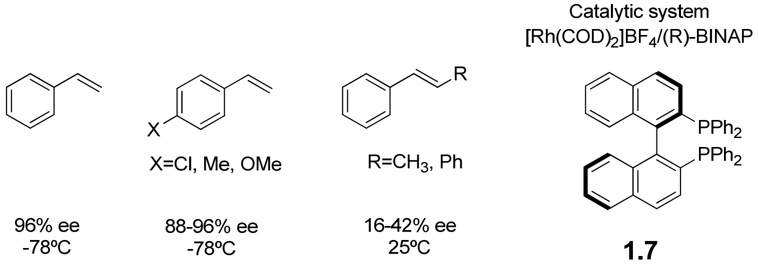


Figure 1.4: Enantioselective hydroboration with [Rh(COD)$_2$]BF_4 and (R)-BINAP

Unlike (R)-BINAP, when [(R)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline] (R)-QUINAP (**1.8**) modified rhodium complexes, the asymmetric induction is high even at room temperature. This is advantageous in the case of sterically demanding substrates, which can be hydroborated with high yields and high levels of enantioselectivity (Figure 1.5).[25]

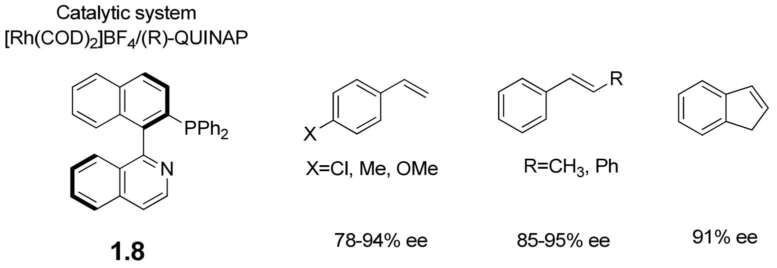


Figure 1.5: Enantioselective hydroboration with $[Rh(COD)_2]BF_4$ and (R)-QUINAP

During the following years, other P,N chiral ligands have been reported. For instance, Chan and coworker[26] synthesized diphenylphosphino-4',6'-di-tert-butyl-1'-phenyl)-3-methylpyridine, PYPHOS (**1.9**), Brown and coworkers[27] prepared 1-(10-(diphenylphosphino)phenanthren-9-yl)isoquinoline, PHENAP (**1.10**), Guiry and coworkers[28] developed 2-phenylquinazolinap (**1.11**), and a P,N-ligand with different backbone was prepared by Chung and coworkers[29] (**1.12**) (Figure 1.6). All contributed to obtain good enantioselectivities in the rhodium mediated hydroboration of vinylarenes.

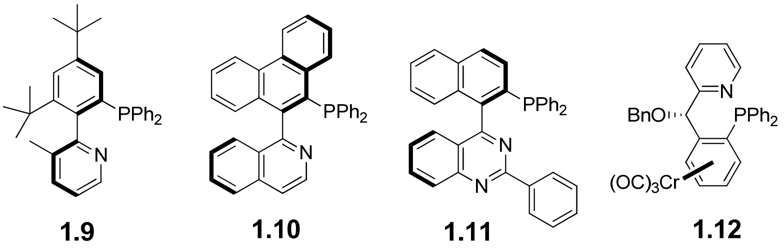
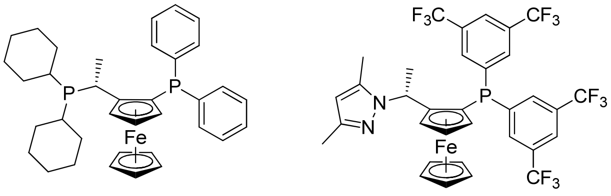


Figure 1.6: Atropoisomeric ligands used in Rh catalyzed asymmetric hydroboration

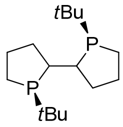
In accordance with the benefits of P,N ligands in rhodium mediated hydroboration of alkenes, Togni and coworkers developed a particularly successful P,N ligand based on the positive influence of the highly effective bisphosphane Josiphos ligand (**1.13**) in rhodium catalyzed hydroboration of styrene (ee>90%)[30] (Figure 1.7). A substantial increase in enantioselectivity has been achieved upon substitution of the PCy_2 in **1.13** with a pyrazoline moiety in **1.14**. This ligand has provided the highest asymmetric induction for the hydroboration of styrene to date (98.5% ee).[31]



1.13 **1.14**

Figure 1.7: P,P and P,N chiral ligands based on the Josiphos type ligands

Recently, enantioselective hydroboration has become a hot topic again. Yun and coworkers[32] developed a new methodology with copper mediated asymmetric hydroboration. Cu(I) with the aid of the chiral diphosphine **1.15**, conducted the hydroboration of styrene with pinacolborane allowing enantiomeric excesses up to 92% (Figure 1.8).

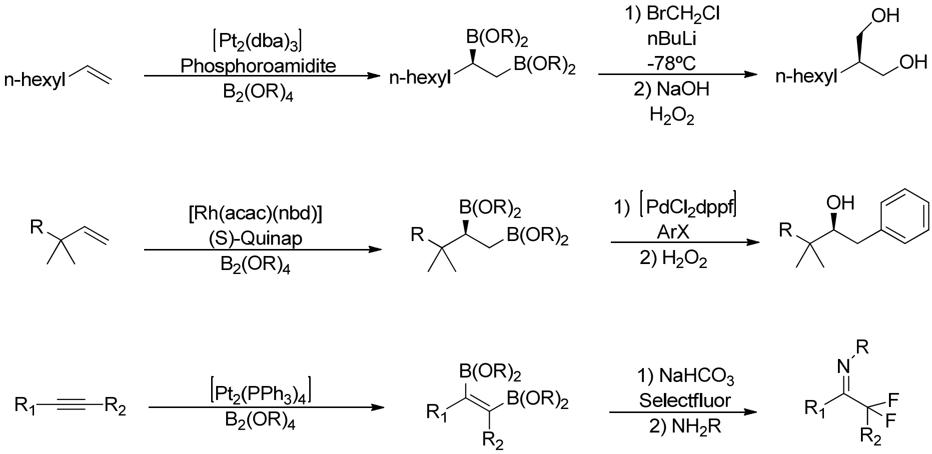


1.15

Figure 1.8: Diphosphine **1.15** used in Cu(I) mediated asymmetric hydroboration of styrene derivatives with pinacolborane

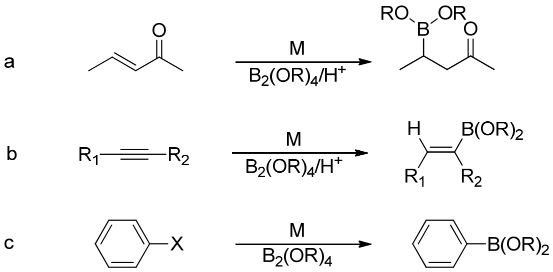
1.3 Diboranes: Reagents and general overview

Diboron compounds are generally used to introduce simultaneously two boryl units in the substrate. The addition to unsaturated carbon-carbon bond proceeds in *syn* fashion. The diboration reaction is an atom economical and very versatile procedure because both boryl units can be transformed independently into different functional groups (Scheme 1.8).[33]



Scheme 1.8: Examples of catalytic diboration reaction and their independently derivatization.

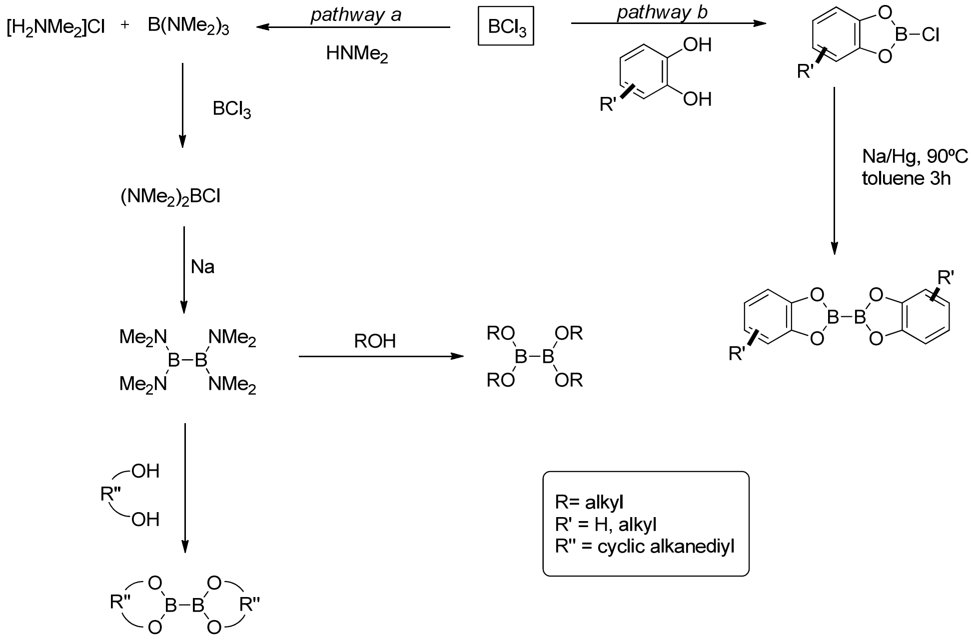
Nowadays, diboron reagents are not only used in diboration reactions. Other reactions utilize them with less atom economy such us β-boration, hydroboration and borylation (Scheme 1.9).



Scheme 1.9: Less atom economical reactions with diboranes: β-boration (a), hydroboration (b) and borylation (c).

Diboron tetrahalides can react with alkenes and alkynes in the absence of a catalyst. However, the diboron tetrahalides are rather difficult to prepare and handle and are unstable towards disproportionation.[34] In contrast, the tetraalkoxidiboron compounds are relatively easy to prepare and are quite stable and easy to handle.

The synthesis of diboranes can involve multiple-step synthesis. One of the best established methods involves the formation of tris(alkylamino)borane as an intermediate (Scheme 1.10, *pathway a*). This synthesis was developed by Noth[35] and Forsyth[36] and improved by Marder[37] and Srebnik.[38] Hartwig and coworkers reported an alternative synthesis from homocoupling of the halocatecholboranes[39] (Scheme 1.10, *pathway b*), failing in the synthesis of tetraalkoxidiboron reagents.



Scheme 1.10: Synthetic routes towards the synthesis of diborane compounds.

Following the described methodologies, a large scope of stable diboron reagents can be synthesized (Figure 1.9). Among tetraalkoxidiborons and bis(catecholato)diboron derivatives, such as bis(catecholato)diboron (B_2cat_2) (**1.20a**), have an increased Lewis acidity due to the positive resonance effect of the electron pair of the oxygen towards the phenyl ring. The reactivity of the diboron is related to the Lewis acidity of the reagent. As a direct consequence, bis(catecholato)diboron is more reactive than bis(pinacolato)diboron (B_2pin_2) (**1.17**) and bis(neopentylglycolato)diboron (B_2neop_2) (**1.18**), despite the fact that B_2cat_2 has the shortest B-B distance (1,678Å (**1.20a**) < 1,711Å (**1.17**) < 2.029Å (**1.18**)).

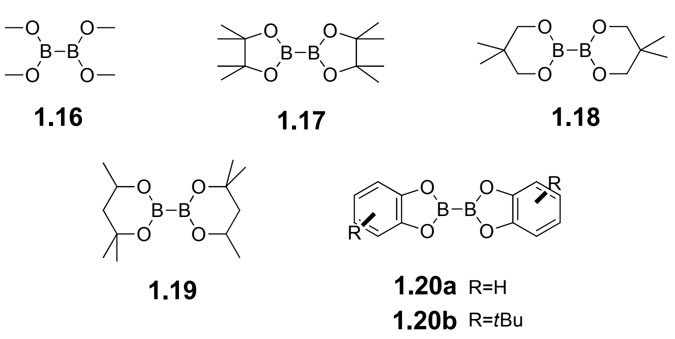


Figure 1.9: Most common diboron reagents

However, diboron reagents cannot be added to alkenes or alkynes in the absence of a catalyst.[40] This is related to the high B-B bond energy (104 kcal·mol^{-1}).[41] For this reason, unlike tetrahalide diborons, the tetralkoxidiborons need to be activated to promote the reaction with unsatured substrates.

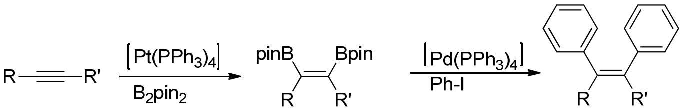
To the best of our knowledge the activation of diborons is mainly performed by transition metal catalyst *via* oxidative addition or *via* transmetallation.

1.3.1 Activation of diboron reagents with transition metal catalysts *via* oxidative addition

The advantage of diborons is that they can be oxidatively added to low-valent transition metals by the B-B bond cleavage, thus allowing the catalytic transfer of the diboron reagent to unsaturated organic substrates,[42] due to the kinetic lability of the resulting boryl-metal complexes. When these two factors are combined, the use of transition metal complexes guarantees, first, the activation of tetraalkoxi- and tetraaryloxydiborons by oxidative addition, and second, the reductive elimination towards the diboron products in a catalytic cycle.[43]

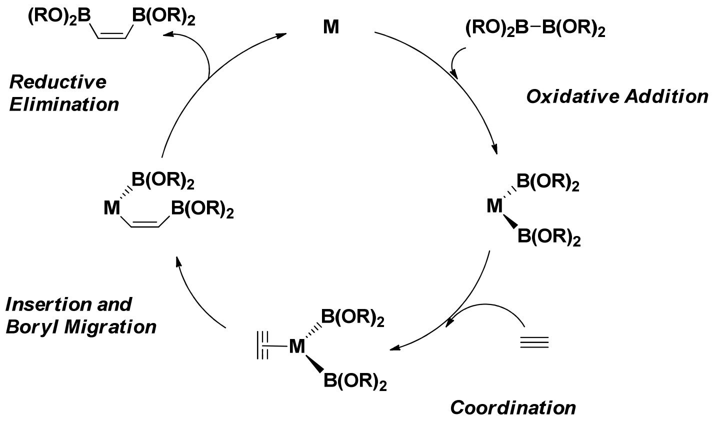
The use of suitable transition metal complexes has other advantages, such as the ability to control chemo- and regioselectively in the formation of the new C-B bonds. Finally, the possibilities of modifying the catalyst precursor with chiral ligands provide an opportunity for the enantioselective formation of new C-B bonds.

The role of the boryl-metal complexes is that they are part of a catalytic cycle in which several consecutive steps transform unsaturated molecules into organomono- and organodiboron compounds.[44] 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 catalyst or borane decomposition can occur. The advantages of metal-promoted 1,2-diboration over the uncatalyzed reaction justifies that researchers have been searching for suitable catalytic systems ever since Miyaura and coworkers's first report.[45] They explored for first time the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors. In their report, they showed that tetrakis(triphenylphosphine)platinum(0) catalyzed the clean addition of bis(pinacolato)diboron to both terminal and internal alkynes, resulting the formation of *cis*-alkene bis-boronate esters. The products obtained in this reaction were transformed through a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 1.11).



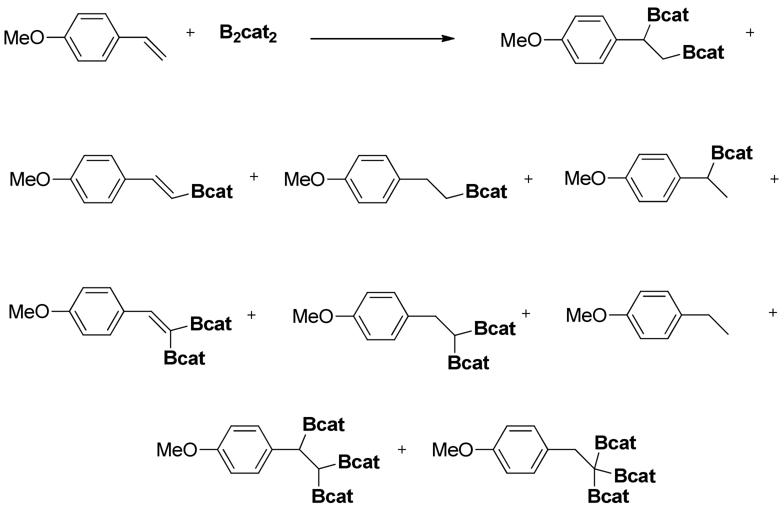
Scheme 1.11: First metal catalyzed diboration reaction reported by Miyaura and Suzuki and their derivatitzation through cross coupling reaction

Miyaura and coworkers also reported spectroscopic evidences for the formation of the *cis*-bis(boryl) complex *cis*-[$Pt(PPh_3)_2(Bpin)_2$], which was isolated and structurally characterized by single-crystal X-ray diffraction confirming that the diboron reagent was added to the metal center *via* oxidative addition. Taking into account this information the authors proposed the following catalytic cycle (Scheme 1.12). The oxidative addition of diboron reagents to the metal center is followed by coordination of the substrate, insertion into the M-B bond and boryl migration, finishing with the reductive elimination that regenerates the active species and provides the diborated product. Subsequent experimental[46] and theoretical studies[47] were in accordance with this proposal.



Scheme 1.12: Catalytic cycle of the diboration reaction

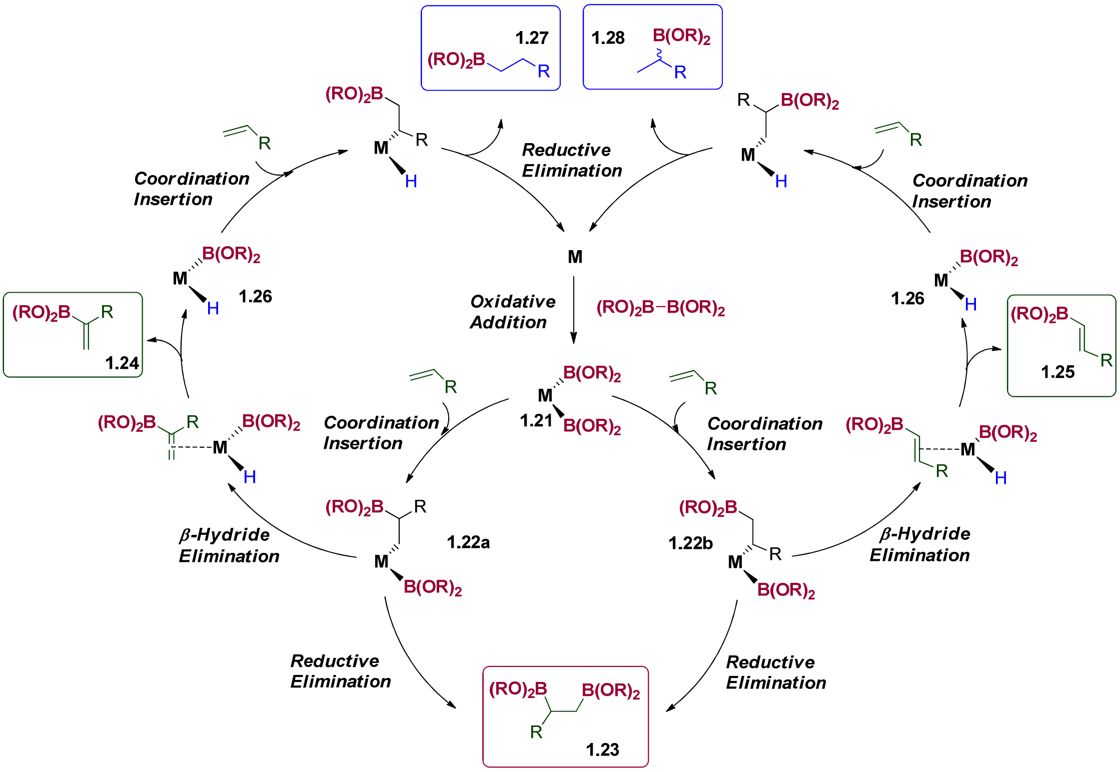
The nature of the catalytic system in diboration reaction is crucial. Both transition metal complexes modified with phosphorous ligands and also phosphine-free metal complexes have been tested,[46] but in all these approaches the catalytic diboration of alkenes gave a complex mixture of organoboron products (Scheme 1.13).[48]



Scheme 1.13: Product distribution observed in Rh(I)-catalyzed diboration of 4-vinylanisole

Deeper analyses of the mechanism revealed the reasons of the side reactions. After substrate coordination to $M(B(OR)_2)_2$ (**1.21**) followed by insertion and boryl migration, two possible intermediates can be formed

(**1.22a** and **1.22b** Scheme 1.14) and reductive elimination provides the diboration product (**1.23** Scheme 1.14). But if β-hydride elimination occurs instead of reductive elimination, alkenylborated byproducts can be formed (**1.24** and **1.25** Scheme 1.14). Hydride boryl metal species (**1.26** Scheme 1.14) can react again with the substrate to generate hydroborated products (**1.27** and **1.28** Scheme 1.14).



Scheme 1.14: Catalytic cycle of the diboration with some of the side reactions

An important aspect of the selective diboration reaction is the nature of the boryl moiety and its influence on the chemoselectivity. The use of bis(pinacolato)diboron (**17**) or bis(neopentylglycolato)diboron (**18**) favors the β-H-elimination versus reductive elimination when the catalyst precursor is *trans*-[Rh(Cl)(CO)(PPh$_3$)$_2$].[49] Alternatively, the activation of B$_2$cat$_3$ (Figure 1.10) by [Rh(acac)L$_2$] provides a zwitterionic complex, which facilitates the reductive elimination towards the diborated product, disfavoring the β-H-elimination step.[50]

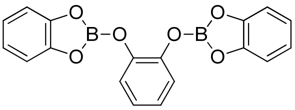
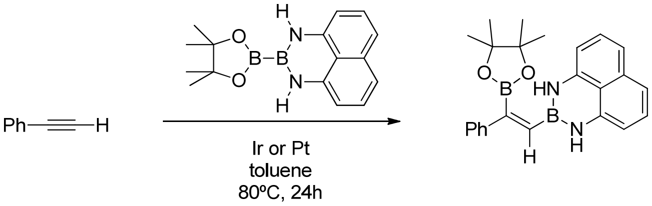


Figure 1.10: Tris(catechol)diboron (B_2cat_3)

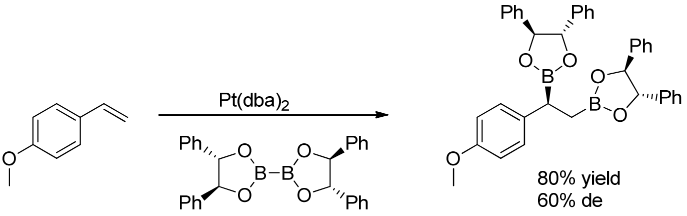
Alternative strategies with different catalytic systems have lead to high chemoselectivities in the formation of organodiboronic esters from C=C, C=N and C=S substrates.[51]

Recently, it has been demonstrated that an unsymmetrical diboron reagents can regioselectively be added to terminal alkynes in the presence of Ir or Pt catalyst, leading to the formation of 1-alkene-1,2-diboron derivatives, in which the internal boryl moiety (Bpin) is more reactive (Scheme 1.15).[52]



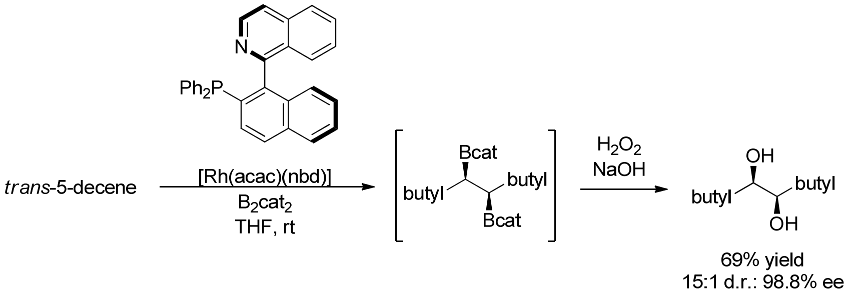
Scheme 1.15: Example of diboration of alkynes with unsymmetrical diboron reagents

The asymmetric catalytic diboration reaction was first carried out using chiral diboron reagents. Marder and coworkers[53] studied the platinum mediated addition of enantiomerically pure chiral diboron compounds to vinylarenes. The reaction was very slow and after 3 days of reaction time at 4ºC, 80% of diboron product was obtained with a diastereomeric excess of 60% (Scheme 1.16).



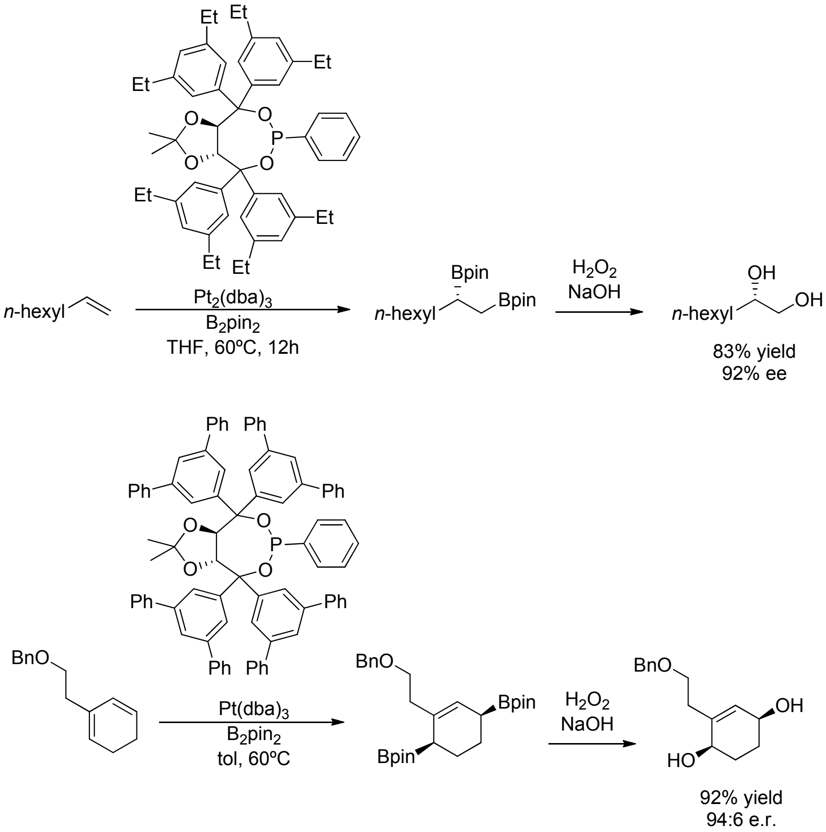
Scheme 1.16: First diastereoselective diboration reaction with chiral diboron reagents

However, the modification of transition metal complexes with chiral ligands opened new doors for asymmetric induction. Morken and coworkers were pioneers in the field of enantioselective diboration reaction of alkenes, by modification of rhodium complexes with the P,N-ligand (R)-QUINAP (Scheme 1.17).[54]



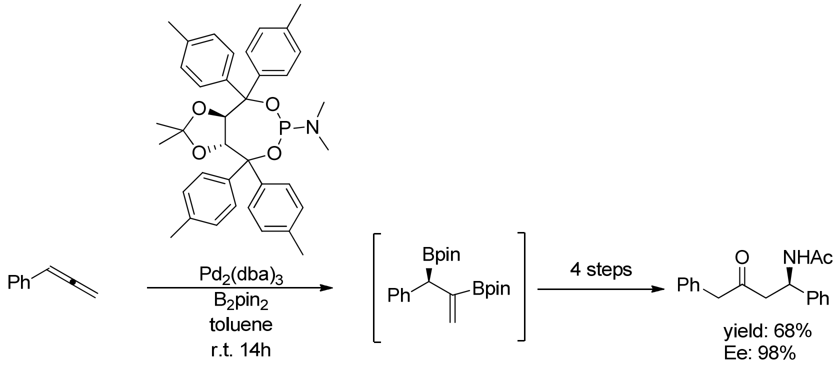
Scheme 1.17: An example of enantioselective diboration of simple alkenes carried out with Rh-QUINAP system

Recently, Morken and coworkes have described a very active and selective Pt catalytic system modified with chiral phosphites (with TADDOL backbone) achieving enantioselectives up to 92% for a large scope of terminal alkenes.[55] Analogous catalytic systems have been recently applied in enantioselective diboration of cyclic dienes.[56] In contrast to the Rh/QUINAP system, which activated bis(catecholato)diboron, the platinum/phosphonite is the first catalytic system providing high enantioselectivity using bis(pinacolato)diboron as the diboron source (Scheme 1.18).



Scheme 1.18: Examples of enantioselective diboration of simple alkenes and cyclic dienes, carried out with Pt-phosphonite system

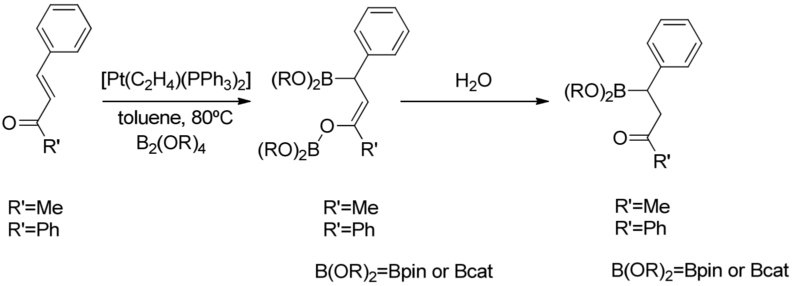
Alternative strategies with different catalytic systems using other metals, such as Pd, and phosphoramidites as chiral ligands have allowed to increase the substrate scope of the enantioselective diboration of allenes (Scheme 1.19).[57]



Scheme 1.19: Enantioselective diboration of allenes with the Pd-phosphoramidite catalytic system

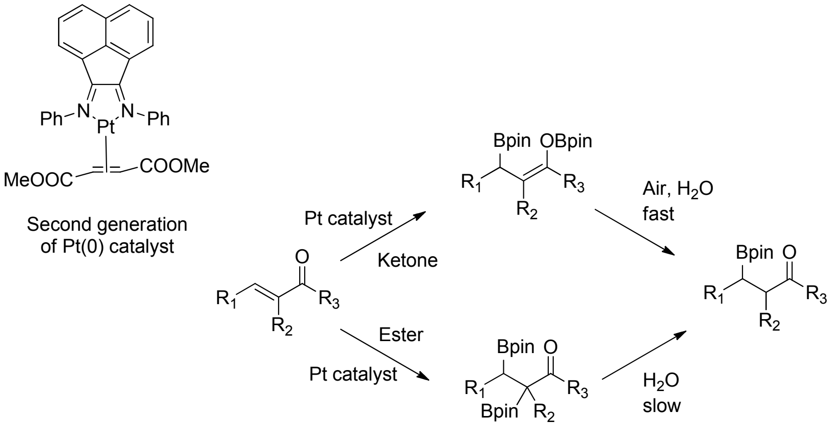
The substrate scope and selective diboration of new substrates have been always a challenge. Activated olefins, such as α,β-unsaturated carbonyl compounds are challenging substrates because the functional groups of the molecule have a direct electronic influence on the double bond. The use of hydroboranes directly reduces the carbonyl group, however the use of diboron compounds allows the β boron addition.

The first diboration of α,β-unsatured carbonyl compounds was carried out by Marder and coworkers[58] with platinum complexes. They described the reaction as a 1,4-diboration reaction, which generated the corresponding β-borated product after the hydrolytic work up (Scheme 1.20). The β-boration reaction has a poor atom economy because only one boryl unit from the diboron reagent is incorporated in the final product.



Scheme 1.20: First β-boration reaction of α,β-unsaturated ketones

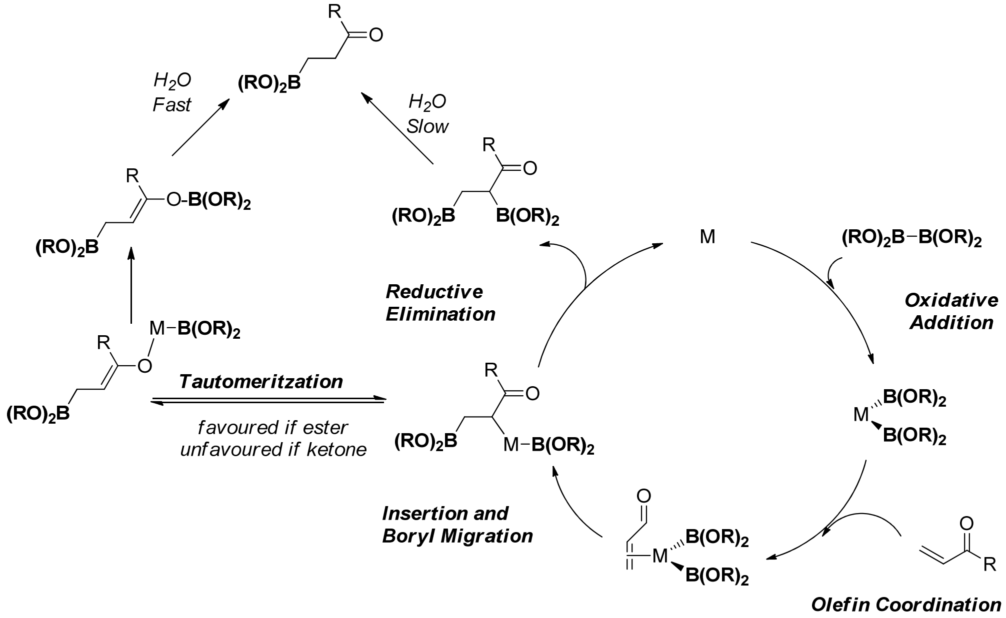
Marder and coworkers[59] focused the efforts on the observation and isolation of diborated intermediates, consequently contributing to the understanding of the mechanisms of the metal catalyzed β-boration reaction. They observed that the second generation of Pt(0) catalyst (Scheme 1.21) displayed different reactivity towards the α,β-unsaturated ketones than esters. The activated ketones gave the expected 1,4-diboration and esters formed the unprecedented 3,4-diborated products.



Scheme 1.21: β-boration of α,β-unsaturated ketones and esters with second generation of Pt(0) catalysts

Kabalka and coworkers, reported in 2002 the β-boration of a large scope of α,β-unsaturated carbonyl compounds (cyclic and acyclic ketones, esters, aldehydes and nitrils) using Wilkinson catalyst.[60]

From the mechanistic point of view, it has been reported that diboron reagents can be added to Rh(I) and Pt(0) via oxidative addition, and the substrate could be coordinated to the metal center, to promote further insertion and consequent boryl migration to the β position (Scheme 1.22): From this point, two possible pathways could be followed, depending on the nature of the substrate: direct reductive elimination to give the 3,4-diborated product, or tautomeritzation followed by the reductive elimination to give the 1,4-diborated product (Scheme 1.22).



Scheme 1.22: Catalytic cycle of β-boration reaction

1.3.2 Activation of diboron reagents with transition metal catalysts *via* σ-bond metathesis

Usually, metals with lower *d* orbital energies fails in the activation of diboron reagents *via* oxidative addition, but some transition metal complexes react with tetralkoxidiboranes without changing the formal oxidation state of the metal. The activation of the diboron reagent can be considered as σ-bond methatesis between the diboron reagent and the M-X unit.

The first copper mediated diboration reaction was previously developed by our group.[61] It was found that Cu(I) complexes modified with NHC (N-heterocyclic carbene) ligands activated bis(catecholato)diboron and promoted a selective addition to alkenes and alkynes. Theoretical DFT calculations were carried out in order to clarify the nature of the interaction between Cu/NHC complexes and B_2cat_2. The results were conclusive in favor of the formation of a sigma complexes, and excluded the possibility of the oxidative addition due to the fact that its activation energy was 69.2 Kcal·mol^{-1} higher than the sigma complex formation (Figure 1.11).

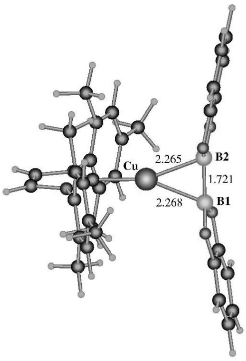
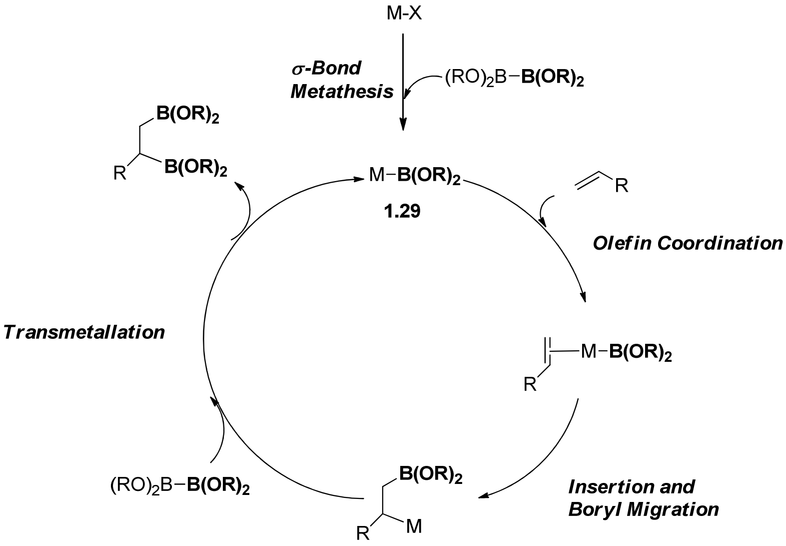


Figure 1.11: Sigma adduct formed between Cu/NHC and B_2cat_2

Catalytic diboration of alkenes with transition metal complexes based on coinage metals was first explored by Marder and coworkers.[48] The catalytic system tested was [Au(PEt_3)Cl]/1,2-bis(dicyclohexylphosphino)ethane, because the gold system, as an example of metal with lower *d* orbital energy, disfavors the β-hydride elimination pathway. The authors found that terminal alkenes could be chemoselectively transformed into the 1,2-diborated products, although high temperatures (80 ºC) and long reaction times (84 hours) were required.

The reaction mechanism might involve the heterolytic cleavage of the diboron reagent by σ-bond metathesis, leading to the formation of the boryl complex, subsequent alkene coordination, insertion and transmetallation with diboron reagent provided the desirable product and regenerated the active species. The generation of the metal-boryl species (**1.29**) is required to start the catalytic cycle (Scheme 1.23)



Scheme 1.23: Plausible catalytic cycle for diboration reaction through σ-bond metathesis

Our group was able to demonstrate that gold(0) nanoparticles stabilized with diphosphines were responsible for the diboration of alkenes, providing complete chemoselectivity towards the 1,2-bis(boronate)esters.[62] Of particular importance are the mild reaction conditions, the low catalyst loading and the substrate scope (Figure 1.12).

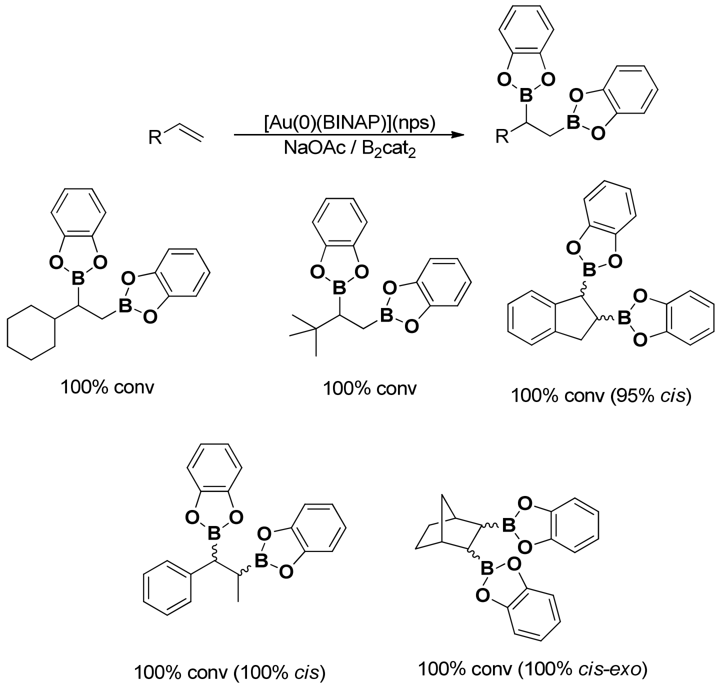
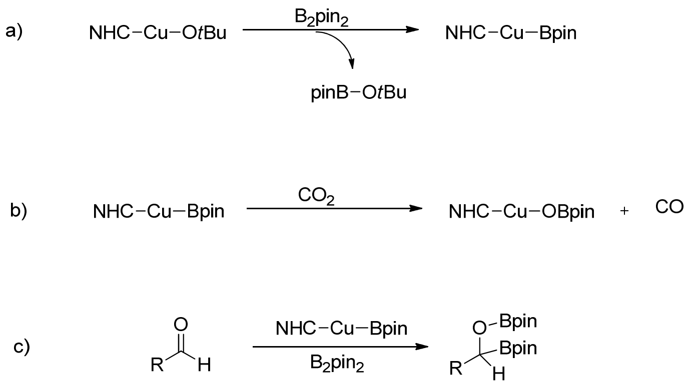


Figure 1.12: Au(0) nanoparticles catalized selecitive diboration of alkenes with B_2cat_2

Alternative catalytic systems based on silver complexes modified with N-heterocyclic carbene ligands have also been found to promote the chemoselective diboration of alkenes.[63]

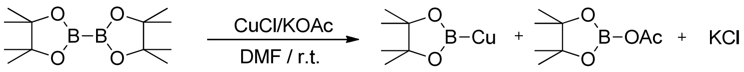
Focusing on the transition metal complexes of group 11, the copper complexes were the preferred ones to explore new approaches towards diboration reaction. In this context, Sadighi and coworkers[64] reported the activation of diborons with Cu(I) salts, and the application of copper-boryl systems in boron addition reactions. The early approach by Sadighi and coworkers was the isolation of LCu-Bpin species (whereby L= N-heterocyclic carbene ligand) from LCu-O*t*Bu and B_2pin_2 through σ-bond metathesis (Scheme 1.24, path a).[64a] Another, important discovery by Sadighi's team involved the use of NHC-Cu-Bpin species in the reduction of CO_2 to CO (Scheme 1.24, path b), and the diboration of aldehydes (Scheme 1.24, path c).[64b]



Scheme 1.24: Sadighi and coworkers approaches towards copper-boryl synthesis and applications

The activation of diboron reagent with copper salts allowed the application of copper salts in β-boration of α,β-unsaturated carbonyl substrates. Miyaura and coworkers,[65] and Hosomi and coworkers[66], at the same time but independently, reported that Cu(I) salts, in the presence of the appropriate additives, catalyzed the β-boration of α,β-unsaturated enones and esters. In both cases the products were obtained after the aqueous work-up, and the possible primary diborated products were not observed.

Miyaura and coworkers used copper chloride as precursor and KOAc as additive. The authors were able to follow the base assisted transmetallation between the CuCl and the B_2pin_2 by H^1 NMR (Scheme 1.25).



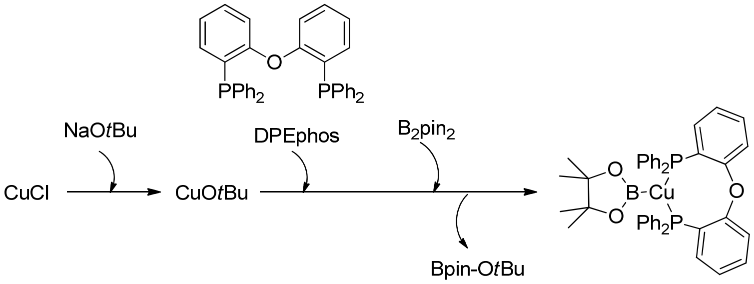
Scheme 1.25: Base assisted transmetallation between B_2pin_2 and CuCl

Hosomi and coworkers used CuOTf as a precursor, and found that the addition of the strongly basic phosphine, PBu_3, was crucial to get an active catalytic system.

Both systems were fairly efficient in the β-boration of α,β-unsaturated carbonyl compounds, although long reaction times were required in order to obtain good yields. This fact was improved only few years ago, when Yun and coworkers optimized the reaction conditions introducing MeOH as an additive to facilitate the recovery of the catalytically active species and provide a H^+ source for the formation of the β-borated product.[67]

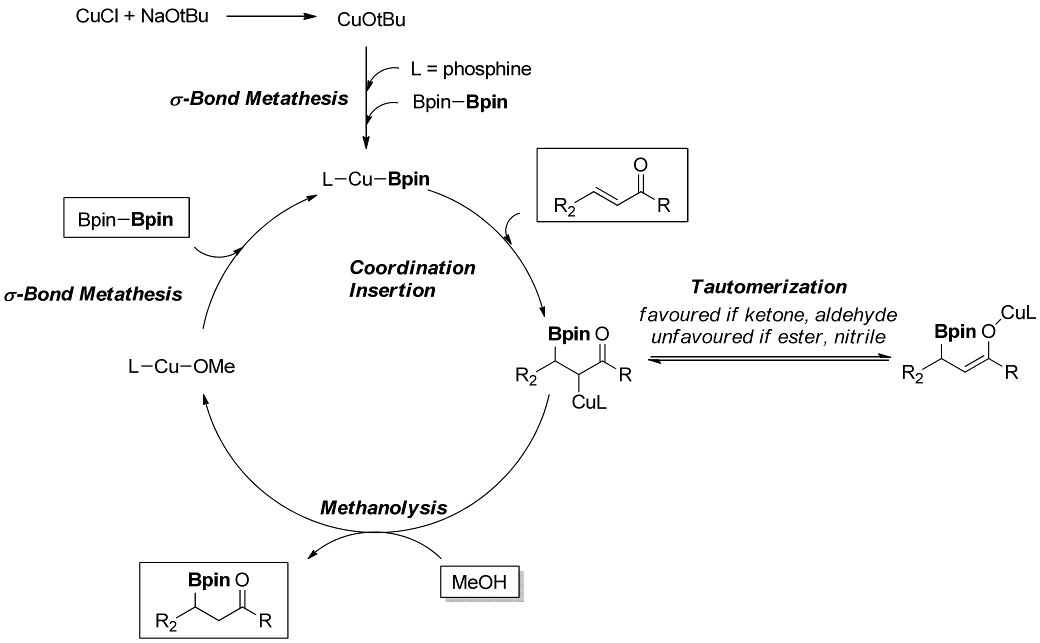
Apart from MeOH, other alcohols were also tested in order to accelerate the reaction and achieve complete conversions with alkenes[67] and alkynes[68] at room temperature in short reaction times. The catalytic system consists of inexpensive copper chloride and phosphine ligand, catalytic amount of base (usually sodium *tert*-butoxide), diboron reagent (B_2pin_2) and methanol.

The authors postulated a mechanism whereby the base activated the CuCl by substitution of the chloride ligand with *t*BuO-, and σ-bond metathesis between the copper-alcoholate and the diboron reagent, B_2pin_2, lead to the catalytically active Cu-Bpin species (Scheme 1.26).



Scheme 1.26: Activation and key catalytic species proposed by Yun and coworkers[67]

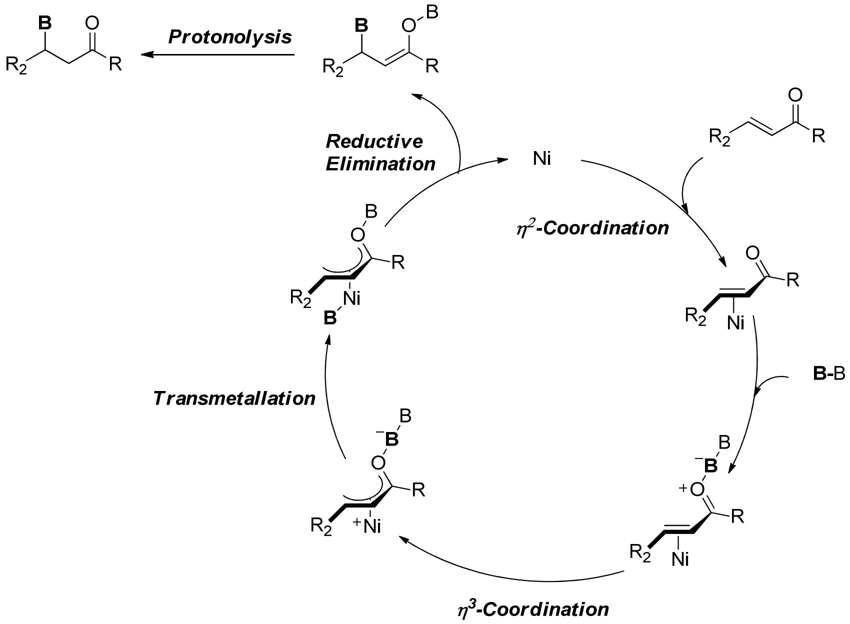
Coordination of the substrate and Michael type migratory insertion resulted in the copper-alkyl complex, which could form the copper-enolate intermediate by tautomerization. Methanolysis of both species provided the product and copper(I)-methoxide, which interacted with B_2pin_2 to regenerate the catalytically active species (Scheme 1.27).



Scheme 1.27: Postulated catalytic cycle of the Cu-catalyzed β-boration reaction of α,β-unsaturated olefins

Lin, Marder and coworkers have carried out a comparative DFT study on the copper catalyzed β-boration of acrolein and methylacrylate.[69] They have shown that both model compounds, the α,β-unsaturated aldehyde and the ester, reacted with copper-boryl complexes through C=C insertion into the Cu-B bond, forming the corresponding Michael addition product. The aldehyde undergoes keto-enol tautomerization and forms the corresponding Cu-enolate, while in the case of the ester the tautomerization did not occur due to the inertness of the ester group.[69]

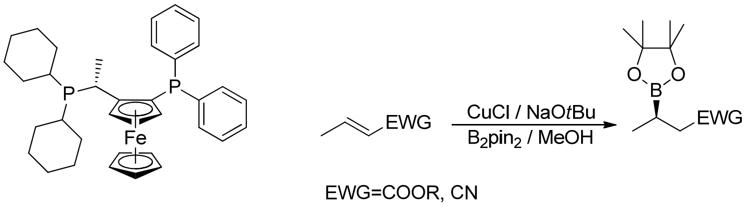
Oshima and coworkers have found that Ni(0) complexes also catalyzed the β-boration of α,β-unsaturated carbonyl compounds.[70] The system, similarly to the Cu(I) catalysts, required the addition of base and alcohol. The authors have proposed a reaction mechanism whereby, as the first step, the substrate coordinated to the Ni(0) precursor via the C=C double bond. After the formation η^2-nickel complex, the coordinated substrate activated the diboron reagent via a Lewis acid-base interaction between the carbonyl functional group and the empty p-orbital of one of the boron atoms (Scheme 1.28).



Scheme 1.28: Postulated catalytic cycle of β-boration of α,β-unsaturated carbonyl compounds with Ni complexes.

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

Despite the increased efforts devoted to the catalytic β-boration reaction, the first enantioselective approach was developed in 2006 by Yun and coworkers,[67] using a chiral diphosphine to modify the copper-boryl catalytic systems. After further optimization, the authors reported in 2008 that ferrocenyl type chiral diphosphines were very efficient to promote high values of enantioselectivity in the β-boration of α,β-unsaturated esters and nitriles (up to 94%) (Scheme 1.29). [71]



13

Scheme 1.29: First enantioselective β-boration reactions

At that point I started my PhD studies, eager to learn more about the activation of diborons and their potential applications to catalytic boron addition reactions. The results of this study of the last four years are summarized in this manuscript.

1.4 Objectives

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

This thesis focuses on the development of new methodologies for boron addition to olefins, with special emphasis on the asymmetric C-B bond formation, but also on the development of tandem reactions and a novel organocatalytic methodology.

The objectives of this study are:

- (NHC)copper mediated β-boration of activated olefins
- Palladium and Iron mediated β-boration reaction and consecutive reactions
- Organocatalytic β-boration of α,β-unsaturated olefins
- Organocatalytic diboration of non-activated alkenes and its enantioselective approach

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The beginning is the most important part of the work.

Plato

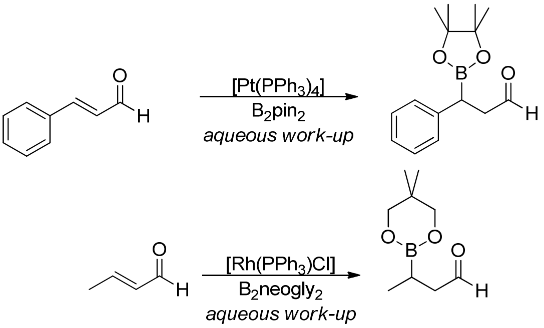
2 (NHC)Copper mediated β-boration of activated olefins

Table of contents

2.1 Introduction

In the course of the development of catalytic diboration of alkenes,[1] the metal-mediated 1,4-addition reaction of diboron reagents to electron deficient olefins has been found to be the most convenient approach towards the preparation of β-boryl carbonyl compounds.[2]

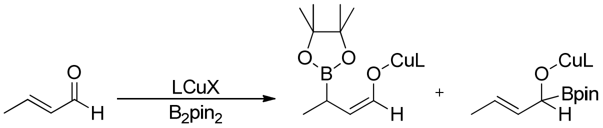
The range of α,β-unsaturated carbonyl substrates that undergo 1,4-addition with bis(pinacolato)diboron (B_2pin_2) is indeed broad.[3] It includes vinylic esters, vinylic ketones, vinylic nitriles, vinylic phosphonates, vinylic sulphonates and extended to acetylenic esters.[4] However, the metal catalyzed β-boration of the most challenging substrates, α,β-unsaturated aldehydes, has previously been reported only in two cases. The first one using Pt[5] as catalysts, and the other one with Rh[6] using the Wilkinson catalyst (Scheme 2.1).



Scheme 2.1: Pt and Rh-catalyzed β-boration of α,β-unsaturated aldehydes

Copper, in contrast to platinum and rhodium, is a cheap, environmentally friendly, air stable and easy to handle metal. Taking into account these advantages and the benefits of copper mediated boron addition reactions, we decided to establish a general methodology for copper-catalyzed β-boration of α,β-unsaturated aldehydes.

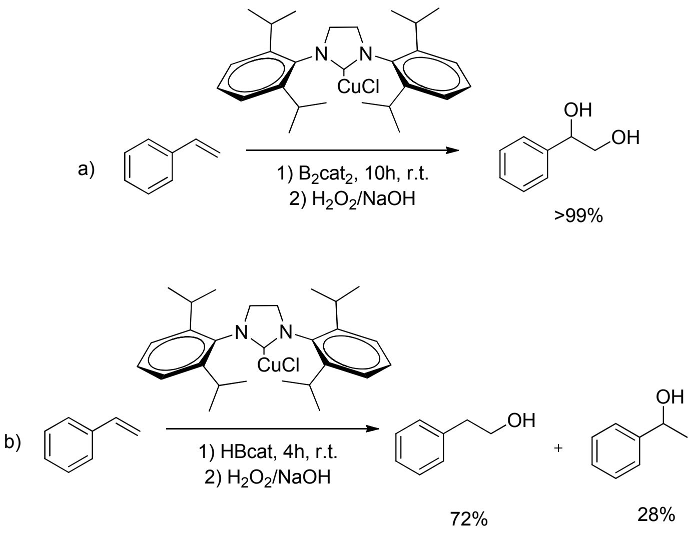
When we defined this objective, we realized that there is an inherent difficulty, the β-boration of aldehydes suffers from the competitive 1,2-diboron addition reaction[7] (Scheme 2.2).



Scheme 2.2: 1,4-addition versus 1,2-addition

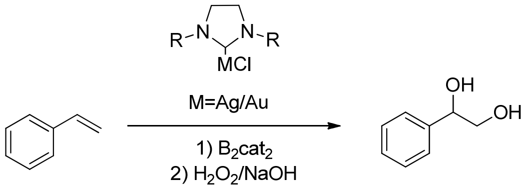
As far as the nature of the ligands in transition metal complexes is concerned, the N-heterocyclic carbenes (NHC) have emerged as a promising family of ligands that could be used to modify transition metal based catalytic systems.[8] This is due to the fact that NHC ligands are versatile and widely modular ligands which form a strong dative sigma bond to the metal.

Our group initiated, few years ago, an interesting study on the use of copper complexes modified with NHC ligands to catalyze diboration and hydroboration of alkenes.[9] The in situ formed NHC-Cu-Bcat species could be the responsible for the complete conversions of vinylarenes into the corresponding 1,2-diboranes in the presence of B_2cat_2. A consecutive work up with $NaOH/H_2O_2$ guaranteed the quantitative conversion to the corresponding diols (Scheme 2.3a). The same NHC-copper complexes mediated the hydroboration of styrene, and a mixture of terminal and internal alcohols were observed after the oxidation work up (Scheme 2.3b).



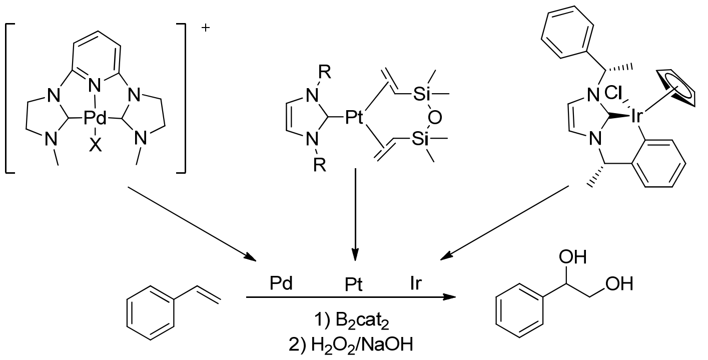
Scheme 2.3: NHC-CuCl mediated a) diboration and b) hydroboration reaction

The use of carbene ligands in boron additions to alkenes was also extended, by our group, to the coinage metals: silver and gold (Scheme 2.4). [10]



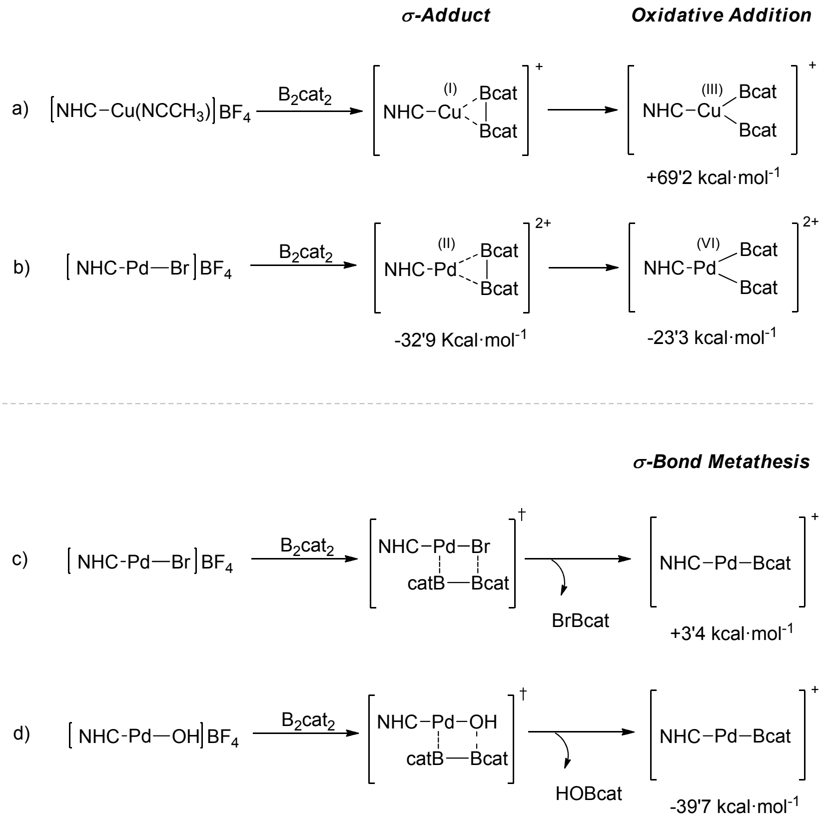
Scheme 2.4: (NHC)Au and (NHC)Ag mediated diboration reaction

The benefits of N-heterocyclic carbene ligands were further explored, by our group, in the diboration of alkenes using other transition metal complexes, such as Pd(II), Pt(0) and Ir(III) (Scheme 2.5).[11]



Scheme 2.5: Pd(II)-NHC, Pt(0)-NHC and Ir(III)-NHC mediated diboration

The gain futher insight into the mechanism in the previous reactions, theoretical studies were carried out, and at least two important points need to be commented. NHC-copper catalytic systems did not activate the diboron B_2cat_2 via oxidative addition, instead the diboron was coordinated to Cu as a B-B σ adduct due to the low energy barrier (69,2 kcal·mol^{-1} lower than oxidative addition) (Scheme 2.6a).[9] Similarly, palladium complexes interacted with B_2cat_2 to form the relatively stable σ-adduct (Scheme 2.6b).[11a] But in contrast to the case of [Cu(NHC) σ-(Bcat-Bcat)]$^+$ where the oxidative addition was discarded, the oxidative addition to the [Pd(NHC) σ-(Bcat-Bcat)]$^{2+}$ is only slightly endothermic by 9.6 Kcal·mol^{-1} with a moderate energy barrier (σ-adduct formation -32,9 kcal·mol^{-1}, oxidative addition -23,3 kcal·mol^{-1}, Scheme 2.6b).[11a] Since this intermediate [Pd(NHC)(Bcat)$_2$]$^{2+}$ is coordinativelly unsaturated, the, alkene coordination could directly take place.

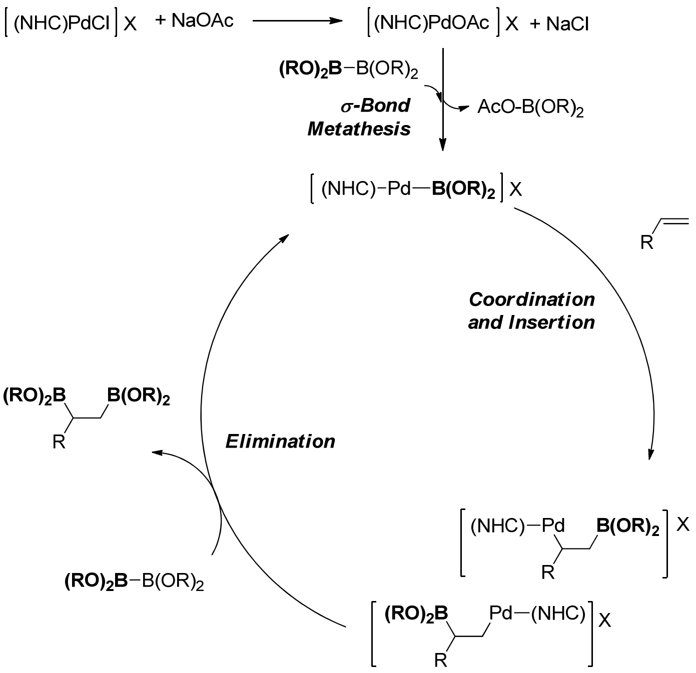


Scheme 2.6: Comparison of energies of the products when $[NHC\text{-}M\text{-}X]^+$ react with B_2cat_2

However, the plausible σ-bond metathesis between the $[NHC\text{-}Pd\text{-}X]^+$ species and diborons was also considered in this previous study. When $[Pd(NHC)Br]^+$ mediated the heterolytic cleavage of B_2cat_2, the overall process was slightly endothermic by 3,4 kcal·mol^{-1} (Scheme 2.6c); but when $[Pd(NHC)(OH)]^+$ was the intermediate for the σ-bond metathesis, the process became highly favorable by -39.7 kcal·mol^{-1} (Scheme 2.6d).[11a]

All these observations were consistent with the experimental results of the catalytic diboration of alkenes mediated by palladium-NHC complexes. Starting from the point that Morokuma and coworkers,[12a,b] and Sakaki and coworkers,[12c] anticipated the lack of catalytic activity of Pd complexes modified with phosphines in diboration of alkenes, when NHC ligands were utilized, a certain degree of reactivity was observed but with low chemoselectivity towards the diborated product.[11a] However the addition of a base to the media (NaOH, NaOAc) increased substantially the conversion of alkenes and only diborated products were observed. This fact might indicate that the base assists the σ-bond metathesis. Therefore a new mechanism was suggested at that time.

The role of the base could involve the displacement of halide substituent from palladium complexes and the promotion of the σ-bond metathesis with the diboron reagent (Scheme 2.7). Once the Pd-boryl complex is formed, insertion of the alkene might result in the formation of the corresponding NHC-Pd-alkyl boryl intermediate that transmetallates with another diboron reagent to regenerate the NHC-Pd-boryl system and produce the 1,2-diborated product (Scheme 2.7).[11a]



Scheme 2.7: Plausible mechanism for palladium mediated diboration *via* σ-bond metathesis

A similar conclusion was reached by Marder and Lin, when they studied from a theoretical point of view, the alkene insertion into (NHC)Cu-boryl species,[13a] and the higher reactivity of B_2cat_2 versus B_2pin_2 in the course of the diboration of alkenes.[13b]

With all these data in mind, we became interested in studying the NHC-copper catalyzed β-boration of α,β-unsaturated carbonyl compounds and exploring the role of the base in promoting the σ-bond metathesis between NHC-Cu-X (X=Cl, OR) and diboron reagents.

2.2 Work hypothesis

Is the base contributing to the preactivation of the catalytic system based on copper modified with NHC ligands? If yes, then can we compare the activity and selectivity of these “preactivated” NHC-Cu-OR catalytic systems, with those obtained with the corresponding non-activated NHC-Cu-X, (X=Cl, BF_4) ?

Once the role of the base is established, and its presence in the reaction is justified, we can progress further examining the induction of asymmetry in the β-boration of α,β-unsaturated carbonyl compounds, by the aid of chiral NHC ligands.

2.3 Results and discussion

We studied the activity and selectivity of a series of NHC-Cu complexes in the β-boration of α,β-unsaturated aldehydes. The catalyst precursors **2.1**-**2.6** (Figure 2.1) were prepared in the laboratory of homogeneous catalysis of the University of Huelva, in collaboration with Dr. M. Mar Diaz-Requejo, following the methods described in the literature.[14] The efficiency of the NHC-Cu complexes was examined in the β-boration of crotonaldehyde with bis(pinacolato)diboron, as a model reaction. Base (NaOtBu) and MeOH were included as additives from the beginning of the study in agreement with the optimized conditions for the β-boration of α,β-unsaturated esters.[3g]

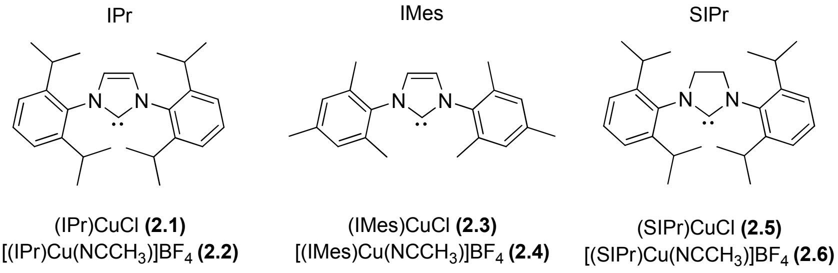
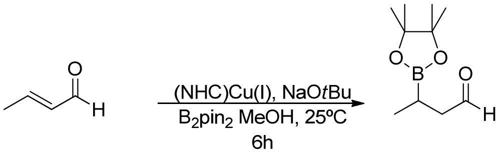


Figure 2.1: Palette of N-Heterocyclic carbenes used in β-boration reaction

The crotonaldehyde substrate was quantitatively consumed in all cases (Table 2.1, entries 1-6) but the chemoselectivity towards the desired β-boryl carbonyl compound was only moderate. The ionic catalytic systems provided poorer chemoselectivities compared to the chemoselectivities achieved with the neutral complexes. The catalyst precursor IMesCuCl, in combination with B_2pin_2, was the most chemoselective (Table 2.1, entry 3), within 6 h, at room temperature, with chemoselectivity up to 60%.

Table 2.1: Screening of (NHC)Cu(I) complexes in the β-boration reaction of crotonaldehyde

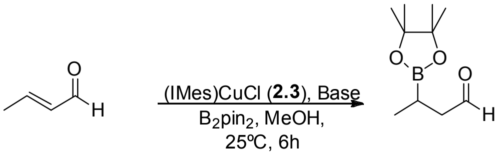


Entry	Precursor of catalyst	Conv (%)	Chemo (%)
1	(IPr)CuCl (**2.1**)	99	52
2	[(IPr)Cu(NCCH$_3$)]BF$_4$ (**2.2**)	99	43
3	(IMes)CuCl (**2.3**)	99	60
4	[(IMes)Cu(NCCH$_3$)]BF$_4$ (**2.4**)	99	39
5	(SIPr)CuCl (**2.5**)	99	48
6	[(SIPr)Cu(NCCH$_3$)]BF$_4$ (**2.6**)	99	39

Standard conditions: Substrate/Cu complex = 0.5 mmols / 0.01 mmols, 3 mol% NaO*t*Bu, 1.1 eq. of bis(pinacolato)diboron (B_2pin_2), 2 eq. MeOH, THF (2 mL), 25 ºC, 6 h. Conversion and chemoselectivity determined by ^{1}H NMR. The 1,2-diborated product was the byproduct.

The crucial role of the base was verified in the β-boration of crotonaldehyde with (IMes)CuCl complex (**2.3**). When the reaction was performed in the absence of base, high conversion of the substrate was achieved but the chemoselectivity was only 33% towards the β-borated product and 67% towards the 1,2-diborated product (**Table 2.2**, entry 4). The addition of inorganic bases such as NaOAc, NaOMe and NaO*t*Bu confirmed their importance, as they enchanced the chemoselectivity up to 60% towards the β-borated product (**Table 2.2**, entries 1-3).

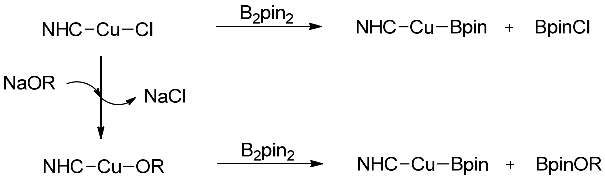
Table 2.2: Screening of bases in the (IMes)CuCl mediated β-boration reaction of crotonaldehyde



Entry	Base	T (ºC)	Conversion (%)	Chemoselectivity (%)
1	NaO*t*Bu	25	99	60
2	NaOMe	25	99	59
3	NaOAc	25	99	41
4	-	25	99	33

Standard conditions: Substrate/Cu complex = 0.5 mmols / 0.01 mmols, 3 mol% base, 1.1 eq. of bis(pinacolato)diboron (B_2pin_2), 2 eq. MeOH, THF (2 mL), 25 ºC, 6 h. Conversion and chemoselectivity determined by ^{1}H NMR. The 1,2-diborated product was the byproduct.

We envisaged the possibility of using (NHC)CuOR as a catalyst precursor. The use of (NHC)CuOR (Scheme 2.8) instead of (NHC)CuCl might benefit the σ-bond metathesis, thus, assisting the β-boration reaction globally, as well.

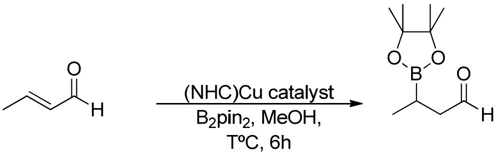


Scheme 2.8: Synthesis of (NHC)CuOR and hypothetical σ-bond metathesis

Additionally, taking into account the described catalytic cycle with the use of this preactivated complex (NHC)CuOR the use of base might be avoided in the catalytic processes. The synthesis of (IPr)CuOMe (**2.7**) and (IPr)CuO*t*Bu (**2.8**) was also carried out in collaboration with Dr. M. Mar Diaz-Requejo at the University of Huelva. The synthesis was based on the reaction of the chloride species with the corresponding sodium alkoxide.

When the catalyst precursor (IPr)CuO*t*Bu was applied in the β-boration of crotonaldehyde in the absence of base, the substrate was transformed into the β-borated product with similar chemoselectivity as in the case of (IPr)CuCl/NaO*t*Bu or [(IPr)Cu(NCCH$_3$)]BF$_4$ / NaO*t*Bu (Table 2.3, entries 1-3). When the temperature was decreased, a slight increase of the selectivity was observed, but, interestingly, increasing of the reaction temperature to 70ºC allowed decreasing the reaction time to 1h, with a concomitant benefit on the chemoselectivity, with values up to 90% in the case of (IPr)CuO*t*Bu (Table 2.3, entry 5) Under the same reaction conditions the (IPr)CuOMe was shown to be as active and chemoselective as (IPr)CuO*t*Bu (Table 2.3, entry 6).

Table 2.3: Comparation of activity and selectivity of IPrCuCl and IPrCuOR in the β-boration of crotonaldehyd



Entry	Catalyst precursor/ additive	Temp (ºC)	Time (h)	Conv(%)	Chemo(%)
1[a]	(IPr)CuCl (**2.1**) / NaO*t*Bu	25	6	99	52
2[a]	[(IPr)Cu(NCCH$_3$)]BF$_4$ (**2.2**) / NaO*t*Bu	25	6	99	43
3[b]	(IPr)CuO*t*Bu (**2.8**) / -	25	6	99	44
4[b]	(IPr)CuO*t*Bu (**2.8**) / -	0	6	99	52
5[b]	(IPr)CuO*t*Bu (**2.8**) / -	70	1	99	90
6[b]	(IPr)CuOMe (**2.7**) / -	70	1	99	84

a) Standard conditions: Substrate/Cu complex = 0.5 mmol /0.01 mmol, 3 mol% of NaO*t*Bu, 1.1 eq. of bis(pinacolato)diboron (B$_2$pin$_2$), 2 eq. MeOH, THF (2 mL), temperature, 6 h. Conversion and chemoselectivity determined by ^{1}H NMR. The 1,2-diborated product was the byproduct b) Carried out in the absence of base.

Two significant advantages were observed when alkoxi copper(I) complexes were used: the higher activity and the higher chemoselectivity towards the β-borated product. Both trends can be seen in the following catalytic profile of the β-boration of crotonaldehyde (Figure 2.2), which compares the activity and the selectivity of (IPr)CuO*t*Bu and [(IPr)Cu(NCCH$_3$)]BF$_4$ / NaO*t*Bu over the course of 80 minutes of reaction time.

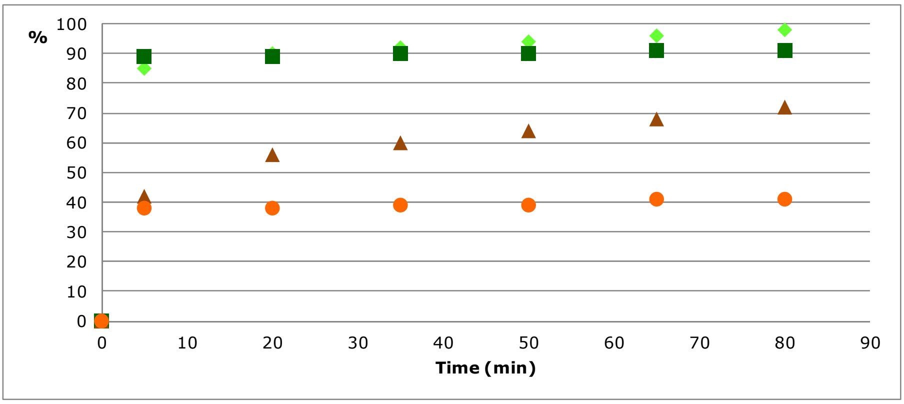
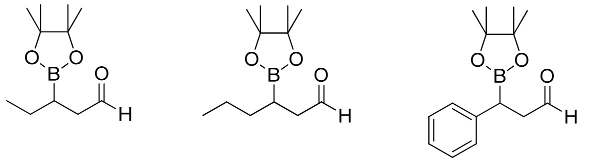


Figure 2.2: Reaction profiles of the β-boration of crotonaldehyde with (IPr)CuO*t*Bu (conversion ♦ and chemoselectivity ■) and [(IPr)Cu(NCCH$_3$)$_3$]BF$_4$ / NaO*t*Bu (conversion ▲ and chemoselectivity ●)

The precursor of catalyst (IPr)CuO*t*Bu and (IPr)CuOMe were also active in the β-boration of related substrates. *trans* 2-Pentenal and *trans*-2-hexenal were converted by (IPr)CuOMe within 1h into the desired β-borated product with high chemoselectivity (Figure 2.3). However, the β-boration of cinnamaldehyde was slower probably due to the steric hindrance of the phenyl ring and/or the conjugation between the C=C double bond and the phenyl ring (Figure 2.3).

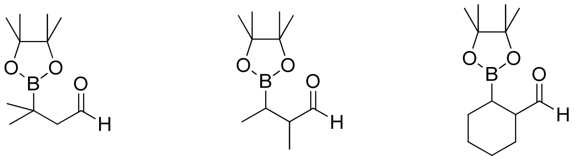
Finally, we studied the β-boration of more sterically hindered α– and β-substituted α,β-unsaturated aldehydes (Figure 2.3). The β,β-substituted 3-methylcrotonaldehyde reacted similarly to crotonaldehyde. However, α-substituted substrates, *trans*-2-methyl-2-butenal did not react even in 16 h of reaction time. Only 1-cyclohexene-1-carboxaldehyde provided a slight conversion with quantitative chemoselectivity towards the desired product, in 16 h (Figure 2.3). The steric environment of the α-substituent of the substrate seems to have a crucial influence on the reaction outcome.



(IPr)CuOMe, 1h
Conversion=99%
Chemoselectivity= 86%

(IPr)CuOMe, 1h
Conversion=99%
Chemoselectivity= 95%

(IPr)CuO*t*Bu, 1h
Conversion=43%
Chemoselectivity= 95%



(IPr)CuOMe, 1h
Conversion=99%
Chemoselectivity= 95%

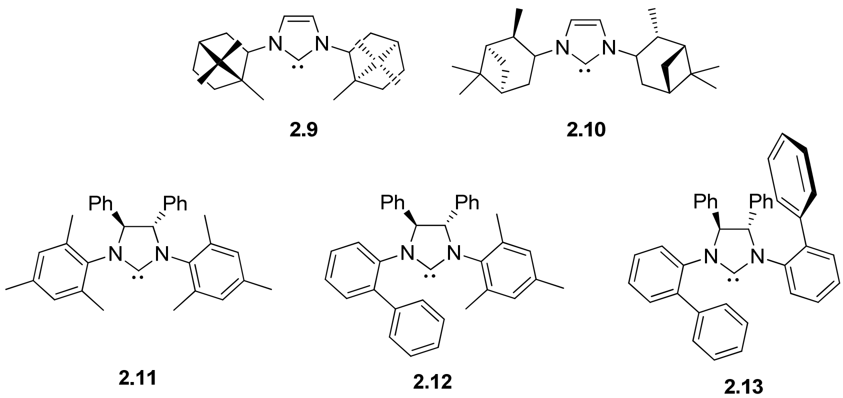
(IPr)CuO*t*Bu, 1h
Conversion=91%
Chemoselectivity= 90%

(IPr)CuO*t*Bu, 16h
No conversion

(IPr)CuO*t*Bu, 16h
Conversion=30%
Chemoselectivity= 92%

Figure 2.3: Substrate scope and influence of α and β substituents in the β-boration of α,β-unsaturated aldehydes

Our next challenge was to extend the methodology to the asymmetric version. Towards this end, we studied the activity and enantioselectivity of (NHC*)Cu(I) catalytic systems with chiral ligands **2.9**-**2.13** in the β-boration reaction of activated olefins. The chiral NHC ligands had been prepared in the laboratory of homogeneous catalysis at the University of Huelva, in collaboration with Prof. P. Perez (Figure 2.4) following a reported methodology.[14]

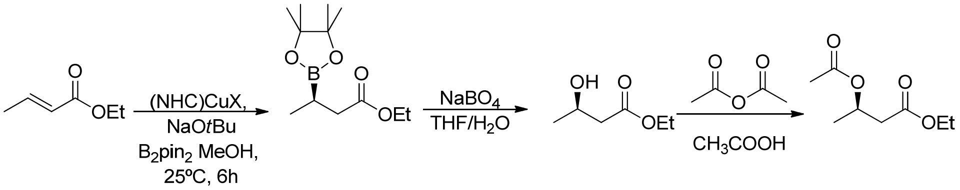


2.9 **2.10** **2.11** **2.12** **2.13**

Figure 2.4: Palette of chiral N-Heterocyclic carbenes used in this study

In the N-heterocyclic carbenes **2.9** and **2.10** (Figure 2.4) the chirality of the ligand origins from the chiral substituents on the N-atoms, both ligands have C_2 symmetry. In ligands **2.11**-**2.13** (Figure 2.4) the centers of the chirality are located on the C_4 and C_5 of the N-heterocyclic carbene. Ligands **2.11** and **2.13** have a two-fold axis and consequently a C_2 symmetry, **2.12** is a C_1, and therefore an asymmetric ligand.

In order to observe how the neutral or ionic nature of the copper complexes influence the activity and selectivity of the β-boration reaction, we employed neutral complexes with the general formula (NHC*)CuCl and ionic complexes with the general formula [(NHC*)Cu(NCMe)]BF_4. These catalyst precursors were employed for the β-boration of the model substrate, ethyl *trans*-crotonate, with B_2pin_2 as the boron source. In addition to 2 mol % of catalyst, the base, NaO*t*Bu (3 mol %) and MeOH (2 equivalents) were also added, in line with the beneficial effect of these additives (Scheme 2.8).



Scheme 2.8: General scheme of chiral β-boration of ethyl *trans*-crotonate followed by oxidation and acylation work up

All the copper complexes led to quantitative conversions and total chemoselectivity towards the β-borated product. When **2.9** and **2.10** ligands were used, the enantiocontrol over the formation of the stereogenic center on the β-carbon was low (Table 2.4, entries 1 and 2). However, complexes with ligands **2.11-2.13** (Table 2.4, entries 3-7) provided moderate ee values. Taking into account this first screening, we could observe that chirality in the backbone of the chiral NHC ligand plays an important role in enchancing the asymmetric induction in the β-boration reaction. Among the ligands with the chirality in the imidazolium core (**2.11**-**2.13**), the ligand with C_1-symmetry (**2.12**) provided better results than ligands with C_2-symmetry (**2.11** and **2.13**). The best result was obtained with the ligand **2.12** bearing a IMes and a biphenyl N-substituent (Table 2.4, entries 5 and 6). It seems that the ionic or non-ionic nature of the precursor does not affect either the conversion or the enantioselectivity. This could be related to the in situ formation of a common catalytic species (NHC)*CuO*t*Bu, which can be generated from both type of precursor complexes under the applied reaction conditions.

Table 2.4: Screening of (NHC)*Cu(I) complexes in β-boration reaction of ethyl *trans*-crotonate.

Entry	Precursor of Catalyst	Conversion (%)	Enantioselectivity (%)
1	[(**2.9**)Cu(NCCH$_3$)]BF$_4$	93	10(R)
2	[(**2.10**)Cu(NCCH$_3$)]BF$_4$	99	16(S)
3	[(**2.11**)Cu(NCCH$_3$)]BF$_4$	99	25(S)
4	(**2.11**)CuCl	96	31(S)
5	[(**2.12**)Cu(NCCH$_3$)]BF$_4$	99	58(R)
6	(**2.12**)CuCl	99	55(R)
7	(**2.13**)CuCl	99	52(R)

Standard conditions: substrate/Cu complex) 0.5 mmol / 0.01 mmol, 3 mol % NaO*t*Bu, 1.1 eq. of bis(pinacolato)diboron (B_2pin_2), 2 eq. of MeOH, THF (2 mL), 25 °C, 6 h. Conversion determined by ^{1}H NMR. Enantioselectivity determined on the acylated product by GC-MS equipped with the chiral column β-cyclodex.

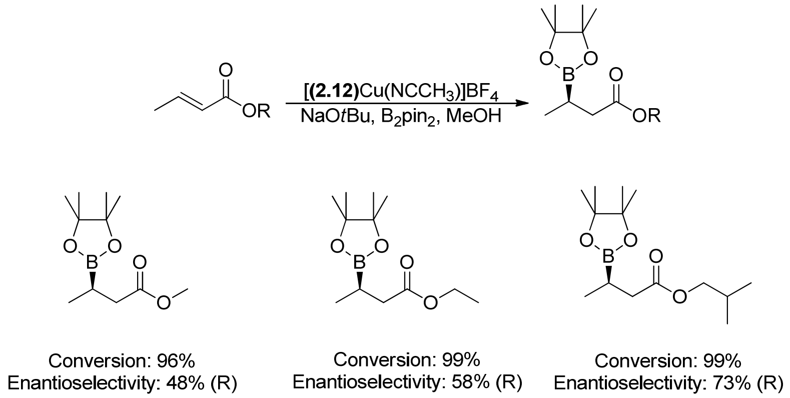
This improvement in the enantiocontrol with chiral (NHC)*CuCl complexes prompted us to analyze the influence of the solvents and base on the β-boration of *trans*-ethyl crotonate. The use of different solvent did not exert any effect on the reaction outcome (Table 2.5). Similarly, when different bases were used, only small differences could be detected in the catalytic activity of (**2.12**)CuCl. However, the absence of base decreases dramatically the conversion, but slightly improves the enantioselectivity.

Table 2.5: Screening of solvents and bases in (NHC)*Cu(I) mediated β-boration reaction of *trans* ethyl crotonate

Entry	Catalyst	Base	Solvent	Conv (%)	Ee (%)
1	(**2.12**)CuCl	NaO*t*Bu	THF	99	55(R)
2	(**2.12**)CuCl	NaO*t*Bu	Toluene	99	59(R)
3	(**2.12**)CuCl	NaO*t*Bu	Acetonitrile	88	52(R)
4	(**2.12**)CuCl	NaO*t*Bu	DCM	96	57(R)
5	(**2.12**)CuCl	NaOMe	THF	99	51(R)
6	(**2.12**)CuCl	NaOAc	THF	73	50(R)
7	(**2.12**)CuCl	NaH	THF	99	53(R)
8	(**2.12**)CuCl	-	THF	<10	63(R)
9	[(**2.12**)Cu(NCCH$_3$)]BF$_4$	-	THF	25	62(R)

Standard conditions: substrate/Cu complex) 0.5 mmol / 0.01 mmol, 3 mol % base, 1.1 eq. of bis(pinacolato)diboron (B$_2$pin$_2$), 2 eq. of MeOH, 2 mL of solvent, 25 °C, 6 h. Conversion determined by ^{1}H NMR. Enantioselectivity determined on the acylated product by GC-MS equipped with the chiral column β-cyclodex.

We extended the metodology to other substrates and we studied the effect of the bulkiness of the ester moiety. The β-boration of methyl *trans* crotonate ester and isobutyl *trans* crotonate ester with [(**2.12**)Cu(NCCH$_3$)]BF$_4$, provided quantitative conversions towards the desired product and the enantioselectivity increased with the bulkiness of the ester moiety (Figure 2.5). These results contradicted the tendency observed by Yun and coworkers,[15] where the enantioselectivity was independent of the nature of the ester moiety when CuCl/(R)-(S)-Josiphos was used as catalyst precursor.



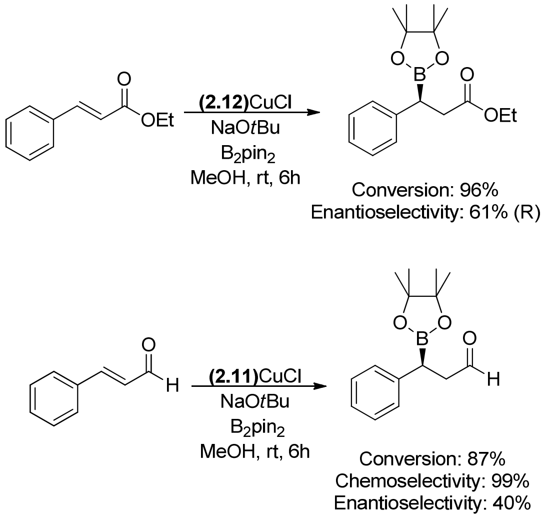
Conversion: 96%
Enantioselectivity: 48% (R)

Conversion: 99%
Enantioselectivity: 58% (R)

Conversion: 99%
Enantioselectivity: 73% (R)

Figure 2.5: Influence of the ester moiety in the (NHC)*Cu(I) mediated α,β-unsaturated esters

The reaction of ethyl cinnamate with (**2.12**)CuCl provided high conversion into the desired product raising the enantiomeric excess up to 61%. The neutral complex (**2.11**)CuCl also afforded high conversion and total chemoselectivity in the β-boration of cinnamaldehyde, with 40% ee. Although the ee value was moderate, this was the first, and still the only, attempt to obtain enantioselectivity in the β-boration of α,β-unsaturated aldehydes (Scheme 2.9).



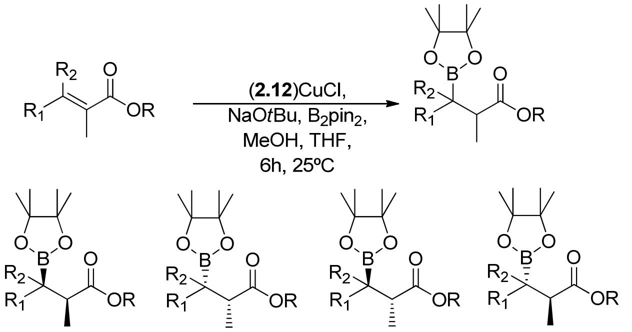
Conversion: 96%
Enantioselectivity: 61% (R)

Conversion: 87%
Chemoselectivity: 99%
Enantioselectivity: 40%

Scheme 2.9: (NHC)*Cu(I) mediated β-boration of ethyl cinnamate and cinnamaldehyde

We have also studied another variable that could affect the degree of enantioselection: the existence of α-substituents in the α,β-unsaturated esters. We have carried out the β-boration reaction of a series of α-methyl substituted esters, such as methyl tiglate (Table 2.6, entry 1), ethyl tiglate (Table 2.6, entry 2), isopropil angelate (Table 2.6, entry 3) and isobutyl tiglate (Table 2.6, entry 4). These experiments have been carried out with the catalyst precursor (**2.12**)CuCl. The quantitative conversions observed in most cases indicated that the α-substitution does not diminish the reactivity of the substrate. The *syn/anti* product ratio is slightly favoured towards the *syn* diasteroisomers, and the ee values were markedly higher for the enantiomeric mixture of the *syn* products than for the *anti* products. The bulkiest isobutyl angelate substrate could be borated at the β-position, with the highest ee value (74%) on the *syn* diastereoisomer (Table 2.6, entry 4).

Table 2.6: (NHC)*Cu(I) mediated β-boration reaction of α-methyl hindered α,β-unsaturated ester



Entry	R	R₁	R₂	Conv (%)	*Syn/anti*	Ee *syn* (%)	Ee *anti* (%)
1[a]	Methyl	Methyl	H	99	60/40	54	5
2	Ethyl	Methyl	H	94	64/36	57	11
3	Isopropyl	Methyl	H	65	55/45	70	20
4	Isobutyl	H	Methyl	93	70/30	74	5

Standard conditions: Substrate/Cu complex = 0.5 mmol / 0.01 mmol , 3 mol% NaO*t*Bu, 1.1 eq. of bis(pinacolato)diboron (B_2pin_2), 2 eq. MeOH, THF, 25 ºC, 6 h. Conversion and chemoselectivity determined by ^{1}H NMR. Enantioselectivity determined on the acylated product by GC-MS equipped with the chiral column β-cyclodex.

2.4 Analysis of the results and limitations

Our current understanding of the NHC-copper(I) mediated β-boration of α,β-unsaturated carbonyl substrates suggests that the catalyst precursor (NHC)CuOR could react with bis(pinacolato)diboron in the absence of base, to promote the formation of the corresponding (NHC)Cu-boryl intermediate easier than (NHC)CuCl. In our study, the base seems to be crucial in assisting the heterolytic cleavage of the diboron via the σ-bond metathesis.

The use of NHC-s as ligands in Cu mediated β-boration of α,β-unsturated aldehydes afforded high conversion of the substrate into the desired β-borated aldehyde, diminishing the 1,2-diboron addition byproduct.

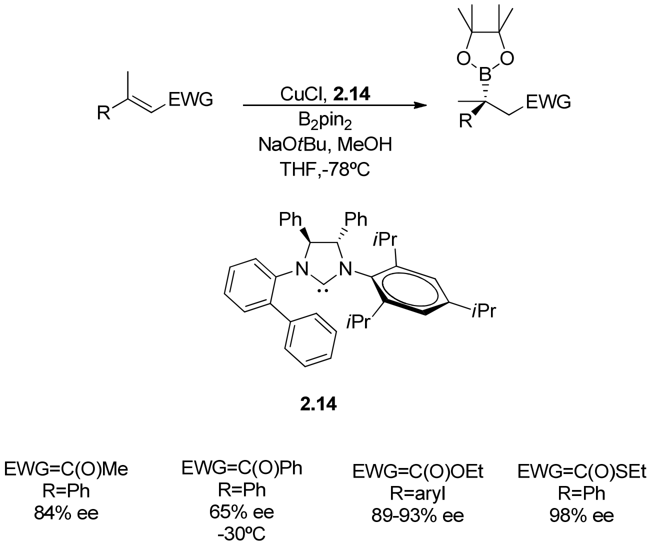
The challenge of enantiofacial differentiation in the conjugate borylation of α,β-unsaturated carbonyl compounds was overcome using copper salts modified with chiral NHC ligands, although the enantiomeric excesses were moderate. Despite this fact, our contribution certainly expanded the portfolio of the stereocontrolled conjugated borylation.

In this work we have demonstrated that NHC chiral ligands could be an alternative to the traditional diphosphine ligands and concluded that a C_1 symmetric NHC ligand induced higher enantioselectivity in the β-boration than the corresponding C_2 analogs.

2.5 Current overview of (NHC)Cu(I) mediated asymmetric β-boration reaction after our contribution

Within this period of time, the copper mediated β-boration reaction has advanced in all aspects. More active and robust catalytic systems have been developed and the substrate scope has been extended.

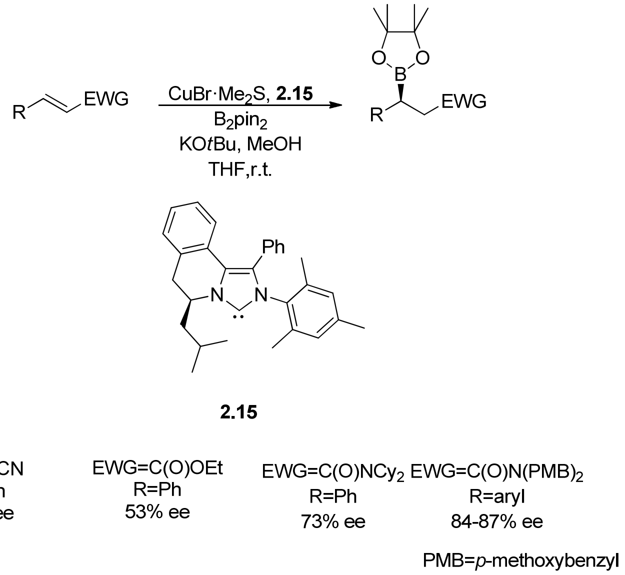
Hoveyda and coworkers,[16] in agreement with our observations about the observed benefits of NHC ligands with *C₁*-symmetry, prepared a similar chiral carbene ligand, **2.14**, cognate of **2.13**, which induced high levels of enantioselectivity in copper catalyzed β-boration of β,β-disubstituted α,β-unsaturated carbonyl compounds (Scheme 2.10), although very low temperatures were required. While ketones gave moderate to good enantiomeric excesses, the reaction of α,β-unsaturated esters and thioesters proceeded with high enantioselectivity. In the case of aliphatic α,β-unsaturated carbonyl compounds the asymmetric induction in the β-boration reaction was reduced.



Scheme 2.10: (NHC)*Cu(I) mediated enantioselective β-boration by Hoveyda and coworkers

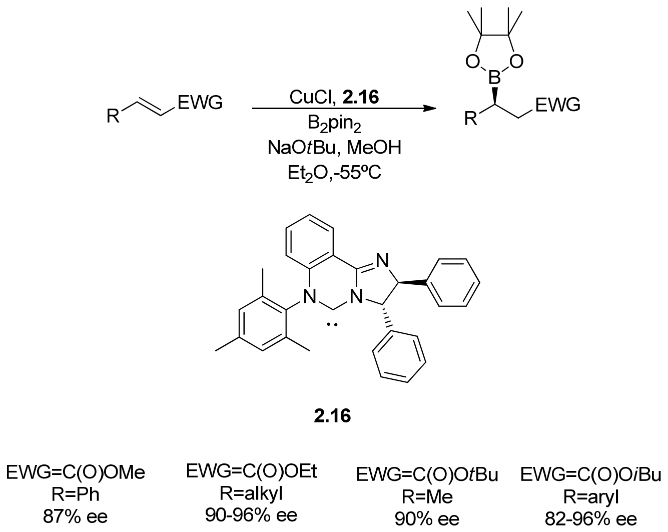
The potential of *C₁*-symmetric NHC ligands in the copper(I) catalyzed 1,4-addition of boron nucleophiles was further demonstrated by Hong and coworkers[17] using the carbene **2.15** as a precursor (Scheme 2.11).

Moderate enantioselectivities have been achieved for β-boration of nitriles and esters but the stereoinduction was improved in the case of conjugated borylation of α,β-unsaturated amides.



Scheme 2.11: (NHC)*-Cu(I) mediated enantioselective β-boration by Hong and coworkers

Recently, McQuade and coworkers[18] introduced a new chiral 6-membered NHC ligand **2.16** to modify CuCl. Generally good enantioselectivities for both alkyl- and aryl-substituted α,β-unsaturated carbonyls were induced, but again low reaction temperatures were required. The activity of catalyst precursor (**2.16**)CuCl was excellent, and catalyst loadings as low as 0,01 mol% still promoted the enantioselective borylation reaction.



Scheme 2.12: (NHC)*Cu(I) mediated enantioselective β-boration by McQuade and coworkers

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Imagination is more important than knowledge.

Albert Einstein

3 Palladium and Iron mediated β-boration reaction

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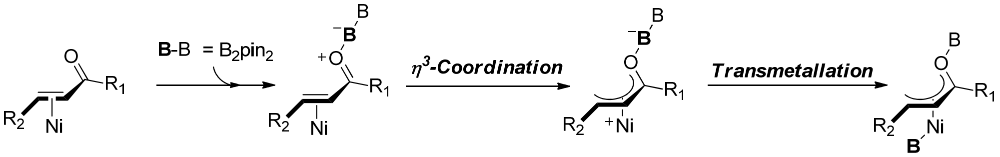
3.1 Introduction

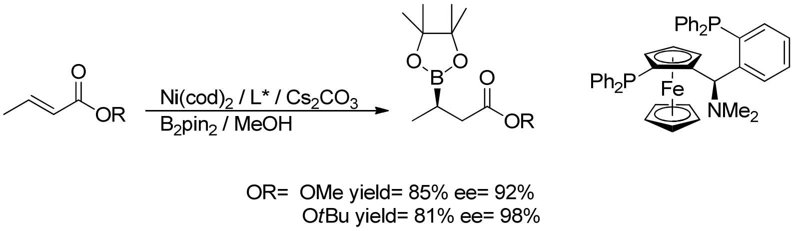
The first catalytic systems that mediated the β-boration reaction of activated olefins were based on Pt(0)[1] and Rh(I)[2] complexes, while the use of copper was first introduced in 2000.[3] It has been suggested that the activation of diboron reagents by copper occurs via σ-bond metathesis meanwhile platinum and rhodium might involve an oxidative addition.

Oshima and coworkers, developed an alternative nickel based catalytic system for the β-boration of α,β-unsaturated carbonyl compounds.[4] From the mechanistic point of view, the authors suggested that the diboron reagent could interact with the carbonyl functional group, in agreement with the Lewis acid properties of the diboronate esters. As a consequence the coordination of the substrate shifted from η^2 to η^3, and allowed the transmetallation step *via* the heterolytic cleavage of the B-B bond. (Scheme 3.1)



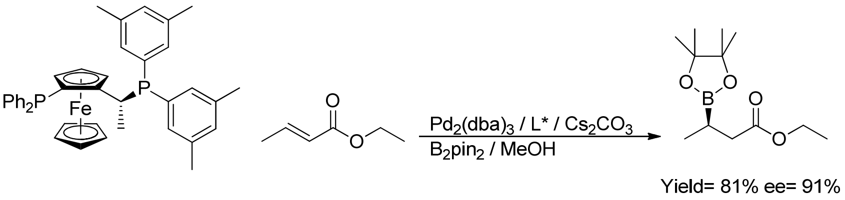
Scheme 3.1: Suggested activation of diboron by Ni(0) catalyst

The authours found that Ni(cod)$_2$ modified with monophosphine ligands mediated the β-boration reaction of di-, tri- and tetrasubstituted α,β-unsaturated esters and amides in high yields.[4] Our group contributed to this field, developing the first Ni mediated asymmetric β-boration of α,β-unsaturated esters, achiving high levels of enantioselectivity[5]. The use of an analog of the catalytic system of Oshima, NiCl$_2$ and Ni(cod)$_2$ modified with the diphosphine (R)-(S)-Taniaphos provided excellent conversions and enantioselectivities up to 96% in the case of Ni(II) and 98% in the case of Ni(0). In this study it was possible to observe a correlation between the asymmetric induction and the bulkiness of the ester functionality. Changing the ester moiety from OMe to O*i*Bu, the enantiomeric excesses increased significantly (Scheme 3.2).



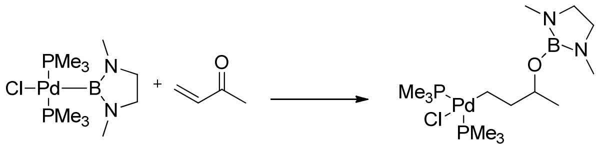
Scheme 3.2: Enantioselective β-boration of α,β-unsaturated ester with Ni(0)/chiral ligands

Although Pt and Ni complexes were found to be effective catalysts for the β-boration of activated olefins, the remaining group 10 metal, Pd, had never been used for this purpose. Our group carried out a series of systematic studies to demonstrate that Pd(0) and Pd(II) could also activate the diboron B$_2$pin$_2$ and promote the β-boration. The use of chiral diphosphines also allowed to induce asymmetry. Pd$_2$(dba)$_3$ modified with (R)-(S)-Josiphos ligands provided total conversions and excellent enantioselectivities up to 91% in the β-boration of α,β-unsaturated esters (Scheme 3.3). The catalytic system formed from Pd(OAc)$_2$/(R)-(S)-Josiphos provided similar conversions but the enantioselectivities were only moderated.



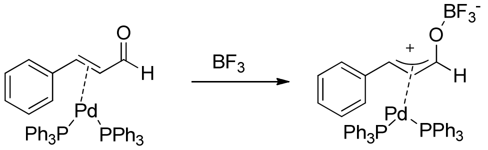
Scheme 3.3: Palladium(0) catalyzed enantioselective β-boration of α,β-unsaturated esters

From a mechanistic point of view, it has been suggested that Pt compounds might activate diborons by oxidative addition, but Ni complexes might involve first the coordination of substrate and then the coordination of the carbonyl functionality to the diboron reagent. In the case of the palladium complexes there had been few precedents, which suggested that the insertion of the α,β-unsaturated ketones into the Pd-B bond proceeded via an alternative 1,4-addition (or insertion step) where the Pd complex was bonded to the β-carbon and the boryl unit to the oxygen (Scheme 3.4).[6]



Scheme 3.4: Stoichiomertric reaction of an α,β-unsaturated ketone with a Pd-boryl complex

Ogoshi and Kurosawa[7] reported that η^2-coordinated palladium complexes with cinnamaldehyde were converted to η^3-coordinated ones in the presence of BF_3 with the aid of the Lewis acidity of the boron (Scheme 3.5). Futhermore, they asserted that the palladium catalyzed 1,4-addition of disilanes to α,β-unsaturated aldehydes and ketones, initiated by Me_3SiOTf, would proceed through a η^3-coordinated intermediates, and not *via* oxidative addition of the Si-Si bond to the palladium complexes.[8]



Scheme 3.5: Change in the coordination mode of cinnamaldehyde to the palladium catalyst in the presence of BF_3

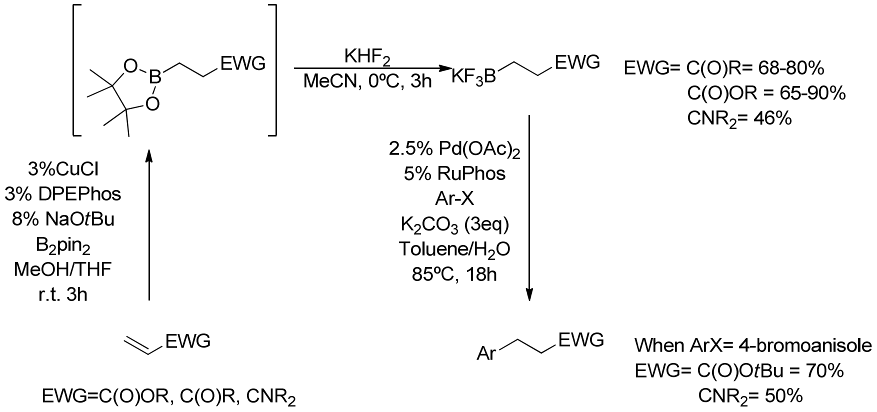
The direction of the insertion found in Pd and Ni precedents seems to be the opposite to that reported by Lin and coworkers[9] (using Cu complexes), with the Pd and Ni fragments taking the role of the nucleophile. However, these differences can plausibly be due to the different behavior of the metal centres, Cu and Pd or Ni, the ligands modifying the metals, the different kind of α,β-unsaturated carbonyl substrates (ketones, aldehydes and esters) or substituents of the double bond (H, alkyl and aryl) as well as the scale. Tanaka and coworkers[6] performed these studies with Pd on a stoichometric scale which allowed the characterization of the thermodynamically most stable products of the insertion.

Marder and coworkers also compiled data on this issue concluding that nucleophilicity is the determining factor in the catalytic pathway with Cu, rather than the oxophilicity of the boron units.[10] They found for Cu-catalyzed reduction of CO_2 to CO that the Cu-C(=O)-O-Bpin species is thermodynamically more stable than the isomeric Cu-O-C(=O)-Bpin, but the former is kinetically inaccessible.

It seems that in the mechanisms of the catalytic β-boration of α,β-unsaturated carbonyl compounds, Pt, Pd, Ni and Cu might play significantly different roles due to the nucleophilicity or oxophilicity of the differents M-B fragments.

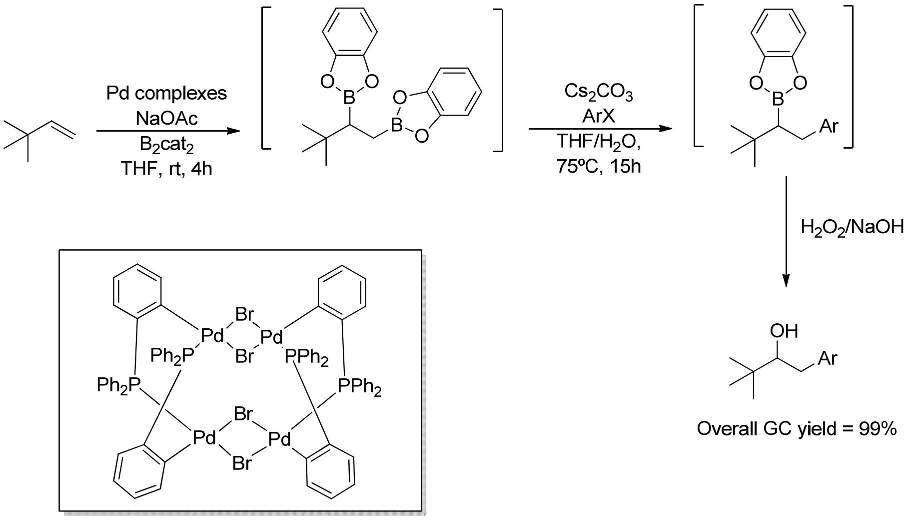
When we started our studies in this field, to the best of our knowledge the direct derivatisation of the β-boryl carbonyl products had only been limited to oxidation/acylation protocols. Taking into consideration the lack of alternative functionalisation methods, we became interested in the selective synthesis of β-boryl carbonyl compounds as a platform for introducing aryl functionalities through cross-coupling reactions.

Cross-coupling reactions of β-boryl carbonyl compounds had only been reported by Molander and coworkers.[11] However a direct funtionalization from the pinacol boryl derivatives was not feasible, and the authors described a method based on the potassium trifluoroborate derivates (Scheme 3.6). The process required two different catalytic systems (Cu(I)/DPEPhos/NaOtBu and Pd(II)/RuPhos/K_2CO_3 ; DPEPhos = [bis(2-diphenylphosphinophenyl) ether] , RuPhos = [2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl] to perform the three steps (Scheme 3.6).



Scheme 3.6: Scheme of β-boration / cross-coupling reaction involving trifluoroborate analogues

In contrast to the previous work of Molander and coworkers, we became interested to perform the β-boration reaction followed by cross-coupling with aryl bromides using a single catalytic system for the two consecutive reactions. In fact, our group had previously performed sequencial reactions with organoboron intermediates. Therefore a series of Pd(II) complexes, synthesized by Prof. M. Angeles Ubeda (University of Valencia), were proved to be very efficient in our hands in the consecutive diboration/arylation reaction sequence (Scheme 3.7).[12]



Scheme 3.7: Example of Pd catalysed consecutive diboration/arylation reaction

Finally, in the light of current debates surrounding sustainable and green chemistry, iron has now become an attractive alternative to the most commonly used expensive noble metals in a number of homogenous catalytic reactions, as it is abundant, inexpensive, less toxic, and environmentally more acceptable.[13] Despite the intense interest in the homogenous catalytic applications of iron complexes, the only known example of iron-mediated C-B bond formation is the 1,4-hydroboration of 1,3-dienes to obtain linear (*E*)-γ-disubstituted allylboranes.[14] Consequently, we became interested in exploring the benefits of iron in the β-boration of electron-deficient olefins, comparing it with the known catalytic systems based on copper, nickel and palladium complexes.

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3.2 Work hypothesis

Since palladium complexes are able to β-borate α,β-unsaturated carbonyl compounds, we wondered whether a palladium catalytic system could perform a consecutive β-boration / cross-coupling reaction sequence. Could the β-pinacolboryl intermediates be suitable organoboranes intermediates for the subsequent Suzuki-Miyaura coupling?

Looking for alternative metals to mediate boron addition reactions to unsaturated substrates, we considered iron as a potential metal to mediate the β-boration reaction. But will iron complexes and salts be able to activate the diboron reagent?

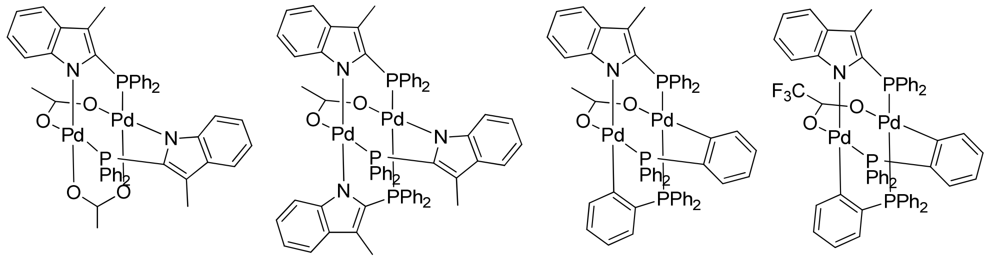
3.3 Results and discussion

An advantage of the palladium-catalyzed boron-addition reaction leading to the formation of a C-B bond is that it is possible to use the organoboronate intermediate to conduct a subsequent palladium-mediated reaction, for example, a cross-coupling reaction[15] or borylative cyclization of enynes and enediynes.[16]

Towards this end, a series of dimeric palladium(II) complexes (**3.1**-**3.4**) had been synthesized by Prof. Ubeda (University of Valencia) and we first tested them in the β-boration of α,β-unsaturated carbonyl compounds.

The four dimeric Pd complexes have the diphenyl (3-methyl-2-indolyl)phosphine ligand in common, which contains an electron rich heterocyclic indole core.[17] Deprotonation of the indolyl nitrogen atom favors the ligand to coordinate as a bidentate ligand with two donor centers of different Lewis basicity. The ligand coordinates to two Pd(II) centers through the P and N atoms to afford the dinuclear complexes due to the geometry and rigidity of the ligand (Figure 3.1).

$[Pd(\mu\text{-}C_9H_7NPPh_2(\mu\text{-}O_2CCH_3))]_2$ (**3.1**) has two bidentate anionic P,N ligands (3-methyl-1-diphenylphosphinoindole) and two acetates while the Pd complex **3.2**,$[Pd(\mu\text{-}C_9H_7NPPh_2)_3(\mu\text{-}O_2CCH_3)]$, have three bidentate anionic P,N ligands and one acetate as bridging bidentate ligand. Complexes $[Pd_2(\mu\text{-}C_6H_4PPh_2)_2(\mu\text{-}C_9H_7NPPh_2)(\mu\text{-}O_2CCX_3)]$ (X=H (**3.3**); X=F (**3.4**)) have two ortho-metalated P,C-ligands (diphenylphosphinobenzene), one anionic P,N ligand and one acetate or one trifluoroacetate (Figure 3.1).



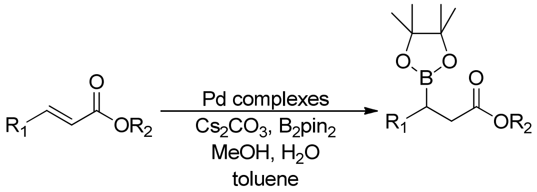
3.1 **3.2** **3.3** **3.4**

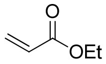
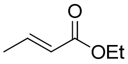
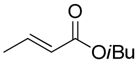
Figure 3.1: Palette of palladium (II) complexes used in this work

To study the palladium-catalyzed β-boration of α,β-unsaturated carbonyl compounds, we selected α,β-unsaturated esters, ketones, aldehydes, and amides as substrates.

The catalytic influence was first established when 2.5 mol% loadings of the dinuclear palladium complexes **3.1**, **3.2**, **3.3**, and **3.4** were used as catalyst precursors in the reactions of the various α,β-unsaturated esters with bis(pinacolato)diboron (B_2pin_2) in toluene (Table 3.1). For ethyl acrylate and ethyl crotonate, the β-boration was complete within 6 h at room temperature regardless of which Pd complex was used as catalyst (Table 3.1, entries 1–9). The presence of a base and MeOH appeared to be crucial for high conversions.[18] THF could be used instead to toluene without loss of efficiency (Table 3.1, entry 5). When a bulkier ester moiety was used as a substrate, we observed a direct influence of the steric proprieties on the reaction outcome. Only the catalytic systems **3.1** provided quantitive conversion within 6h (Table 3.1, entry 10).

Table 3.1: Pd complexes mediated the β-boration of ethyl acrylate, ethyl crotonate and isobutyl crotonate

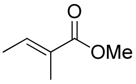
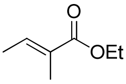
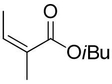
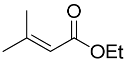


Entry	Substrate	Catalyst precursor	Time (h)	Conversion (%)
1		**3.1**	6	99
2		**3.2**	6	99
3		**3.3**	6	99
4		**3.4**	6	99
5[a]		**3.1**	6	99
6		**3.1**	6	99
7		**3.2**	6	99
8		**3.3**	6	99
9		**3.4**	6	99
10		**3.1**	6	99
11		**3.2**	6	64
12		**3.3**	6	47
13		**3.3**	24	57
14		**3.4**	6	81

Standard conditions: substrate / Pd = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 eq), Cs_2CO_3 (1.5 eq.), H_2O (1.5 eq.), MeOH (1 eq), solvent: toluene (2 mL); T=25ºC. Conversion determined by ^1H NMR. a) Solvent: THF (2 mL).

A similar trend correlated with bulkiness of the ester moiety was observed with α-subtituted, α,β-unsaturated esters. When the catalyst precursor **3.1** mediated the β-boration of methyl tiglate (Table 3.2, entry 1), the β-borated product was obtained in 94% of conversion. When more hindered substrates were used (ethyl tiglate and isobutyl angelate) the conversion decreased when the steric hindarance was higher (Table 3.2, entries 2-3). This trend was not observed in the case of the β-substituted α,β-unsaturated esters which could be quantitatively transformed into the desired β-borated product within 6h Table 3.2, entry 4).

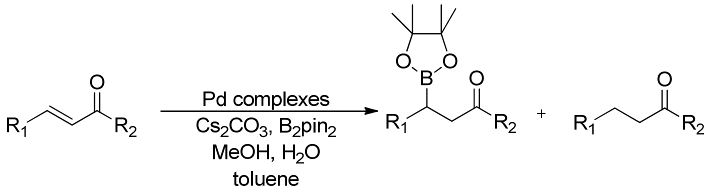
Table 3.2: Pd complex **3.1** mediated the β-boration of α or β substituted α,β-unsaturated esters

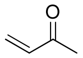
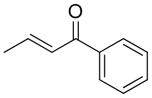
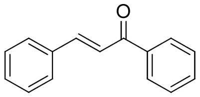
Entry	Substrate	Catalyst precursor	Time (h)	Conversion (%)
1		**3.1**	6	94
2		**3.1**	16	50
3		**3.1**	24	27
4		**3.1**	6	99

Standard conditions: substrate / Pd = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 equiv), Cs_2CO_3 (1.5 eq.), H_2O (1.5 eq.), MeOH (1 eq.), solvent: toluene (2 mL); T=25ºC. Conversion determined by ^{1}H NMR.

We next explored the β-boration of related α,β-unsaturated ketones, which have only been explored previously in the literature with Cu(I) salts as catalytic system.[19] The catalyst precursor **3.1**-**3.4** mediated the β-boration of methyl vinyl ketone, in toluene and THF, providing complete conversions (Table 3.3). However when (*E*)-4-phenylbut-3-en-2-one or *trans*-chalcone were used as substrate, the conversion and chemoselectivity diminished and the formation of the non-borylated saturated byproduct was observed (Table 3.3, entries 6-9).

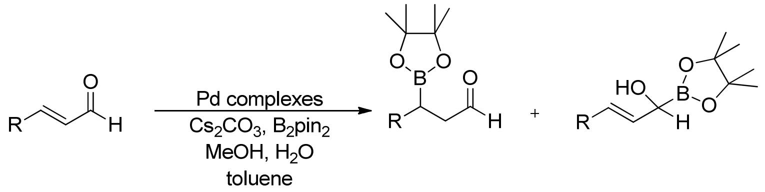
Table 3.3: Pd complexes mediated β-boration of α,β-unsaturated ketones



Entry	**Substrate**	**Catalyst precursor**	**Conversion (%)**	**Chemoselectivity (%)**
1		**3.1**	99	99
2		**3.2**	99	99
3		**3.3**	99	99
4		**3.4**	99	99
5[a]		**3.1**	99	99
6		**3.1**	85	65
7		**3.3**	80	76
8		**3.1**	93	64
9		**3.3**	93	71

Standard conditions: substrate / Pd = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 equiv), Cs_2CO_3 (1.5 equiv), H_2O (1.5 equiv), MeOH (1 equiv), solvent: toluene (2 mL), T=25ºC. Conversion and chemoselectivity determined by ^1H NMR spectrometry. a) Solvent: THF (2mL)

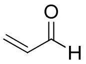
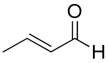
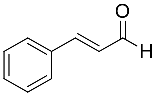
We next focused in the β-boration of α,β-unsatured aldehydes with particular interest to study the influence of the palladium complexes into the chemoselectivity.[2,20,21] (Scheme 3.8).



Scheme 3.8: Pd mediated β-boration of α,β-unsaturated aldehydes

When we explored the β-boration of acrolein with the dimeric palladium complexes, we found that the catalytst precursor **3.1** provided total conversion and chemoselectivity towards the 1,4-addition (Table 3.4, entry 1). The catalytst precursor **3.2** and **3.4** were less selective under identical reaction conditions. The complex **3.1** was proved to be very effective in catalyzing the β-boration of crotonaldehyde (Table 3.5, entries 5 and 6), and even in the absence of MeOH/H_2O as additives the system was slightly more selective. On the other hand, when MeOH and water were not added to the system, the β-boration of cinnamaldehyde with the complex **3.1** was more selective but the activity decreased significantly (Table 3.4, entries 7-8).

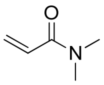
Table 3.4: Pd complexes mediated β-boration of α,β-unsaturated aldehydes

Entry	Substrate	Catalyst precursor	Additives	Conv (%)	Chemo (%)
1		**3.1**	MeOH/H_2O	94	98
2		**3.2**	MeOH/H_2O	82	74
3		**3.4**	MeOH/H_2O	97	87
4[a]		**3.1**	MeOH/H_2O	91	95
5		**3.1**	MeOH/H_2O	97	83
6		**3.1**	-	96	92
7		**3.1**	MeOH/H_2O	75	23
8		**3.1**	-	51	99

Standard conditions: substrate / Pd = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 eq.), Cs_2CO_3 (1.5 eq.), H_2O (1.5 eq.), MeOH (1 equiv), solvent: toluene (2 mL), T=25ºC. Conversion and selectivity determined by ^{1}H NMR. a) Solvent: THF (2 mL).

The metal-catalyzed β-boration of α,β-unsaturated amides was first performed by Oshima and coworkers[4] using Ni(II) complexes. It was revealed that amides reacted with B_2pin_2 much more rapidly than the corresponding esters. The asymmetric version was developed by Yun and coworker[22] using Cu(I) catalytic systems modified with chiral bidentate ligands. In this context, we became interested to explore for the first time whether palladium complexes could efficiently perform the conjugate B addition to α,β-unsaturated amides. We found that the dimethyl acrylamide, could be quantitively converted into the corresponding β-borated product within a reasonable reaction time (6h), at room temperature, in both toluene and THF (Table 3.5, enties 1 and 5).

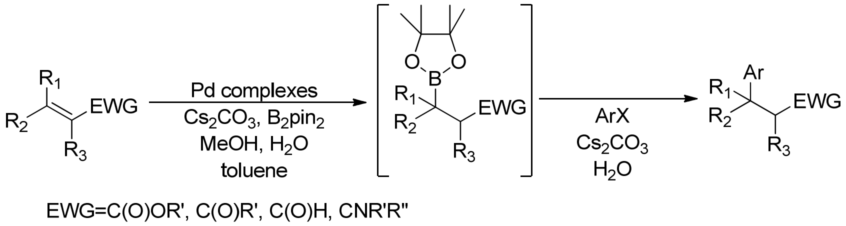
Table 3.5: Pd complexes mediated the β-boration of amides

Entry	Substrate	Catalyst precursor	Time (h)	Conversion (%)
1		**3.1**	6	99
2		**3.2**	6	83
3		**3.3**	6	99
4		**3.4**	6	66
5[a]		**3.1**	6	99

Standard conditions: substrate / Pd = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 eq.), Cs_2CO_3 (1.5 eq.), H_2O (1.5 eq.), MeOH (1 eq.), solvent: Toluene (2 mL), T=25ºC. Conversion determined by ^{1}H NMR. a) Solvent: THF (2 mL).

At this point we could establish that the complex **3.1** catalyzed efficiently the β-boration of a wide range of activated olefins, and the high activity that we observed could be due to a synergy between steric and electronic properties.

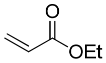
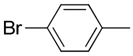
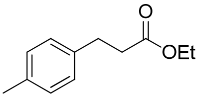
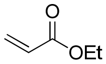
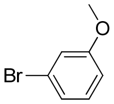
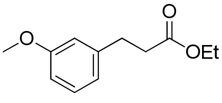
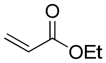
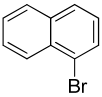
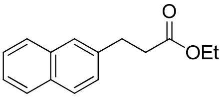
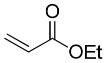
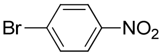
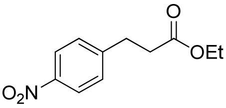
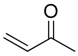
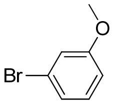
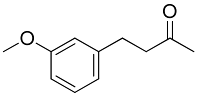
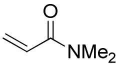
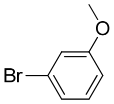
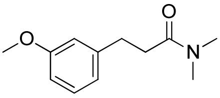
Considering the benefits of palladium-mediated β-boration reactions, we next became interested in studying whether palladium-based complexes could be used to catalyze, in a single-pot, the β-boration/Suzuki–Miyaura cross-coupling reaction sequence using only 2.5 mol% of a given palladium dinuclear complex for the whole consecutive reactions (Scheme 3.9).



Scheme 3.9: Pd mediated the single pot β-boration/cross coupling reactions

We were very pleased to observe that complex **3.3** catalyzed both the β-boration of ethyl acrylate or methyl vinyl ketone and the subsequent cross-coupling with a range of aryl bromides although conversions were only moderate after 24h of reaction time (Table 3.6). However only one β-boration/cross-coupling reaction sequence proceeded to completion when dimethyl acrylamide was the substrate and 3-bromoanisole was the aryl halide (Table 3.6, entry 6). THF was the solvent of choice for the two consecutive reactions instead of toluene, because it increased the efficiency of the cross-coupling transformation.

Table 3.6: Complex **3.3** mediated the β-boration/cross-coupling reaction

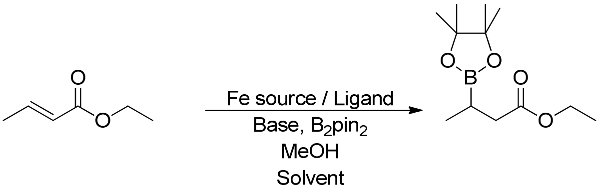
Entry	Substrate	ArX	Product	Conv[a] (%)
1				31
2				28
3				14
4				55
5				46
6				99(89)[b]

Standard conditions for β-boration: substrate / Pd complex **3.3** = 0.125 mmol / 0.003 mmol; B_2pin_2 (1.5 eq.), Cs_2CO_3 (1.5 eq.), H_2O (1.5 eq.), MeOH (1 eq.); solvent: THF (2 mL), T=25ºC, t=6 h. Standard conditions for cross-coupling: ArX (2 equiv) and Cs_2CO_3 (3 equiv), reflux for 24 h. Conversion determined by ^1H NMR spectrometry. a) Conversion of the β-borated intermediate formed quantitatively in the first step. b) Isolated yield.

As we previously mentioned in the introduction of this chapter, cross-coupling reaction of borilate amides has only been reported by Molander and coworkers.[11] This method involved two catalytic systems and three synthetic steps, and resulted in moderate overall yields. We have improved this methodology, using a single catalytic system that involves two synthetic steps with a full conversion in both steps, and obtaining an overall yield up 89%, for the dimethyl acrylamide.

In our ongoing research study, we found that palladium complexes could show multifaceted catalytic properties. Complex **3.3** participated in different catalytic cycles involving organoborane intermediates with equal efficiency. Next, we wanted to progress with our search to find inexpensive transition metals that could also promote the β-boration reaction. Iron raised our interest, since it is cheap, environmentally friendly, and was unexplored for catalyzing conjugated boron addition reactions.

We started our study exploring whether the addition of iron salts had any positive influence on the β-boration of α,β-unsaturated esters with diboron reagents. Therefore, we selected bis(pinacolato)diboron (B_2pin_2) as the boron source, methanol as the proton source and ethylcrotonate as the substrate for the model β-boration reaction (Scheme 3.10).

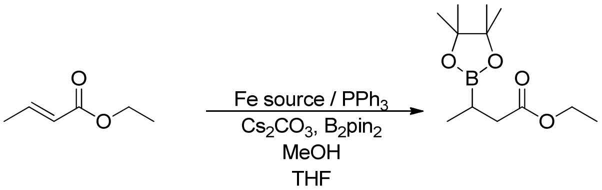


Scheme 3.10: General scheme of iron mediated β-boration of ethyl crotonate

The readily available iron(II) and iron(III) salts, $Fe(acac)_2$ (acac=acetylacetonate), $Fe(acac)_3$, $FeCl_2$, and $Fe(OMe)_2$ were selected as iron sources (2 mol% of iron loading). However, none of these salts were able to catalyze the β-boration of the ethyl crotonate, even at 70ºC, in the absence of base (Table 3.7, entries 1-5). However, the addition of a base (Cs_2CO_3) to the reaction medium promoted the β-boration of ethylcrotonate (Table 3.7, entries 6-9). The positive influence of base in boron conjugated addition was first observed in the case of the CuCl/KOAc mediated β-boration of α,β-unsaturated carbonyl compounds.[3a,b]

The phosphine modified system $Fe(acac)_2/PPh_3$ ($Fe/PPh_3=1:2$) was also inactive in this reaction, however the sole addition of 3 mol% of base allowed the complete β-boration of ethyl crotonate within 24h (Table 3.7, entry 10). Interestingly, when we increased the amount of base, an enchanced activity was observed (Table 3.7, entries 10-13). Therefore when the catalytic system $Fe(acac)_2/PPh_3$ ($Fe/PPh_3=1:2$) was used in the presence of 15 mol % of Cs_2CO_3, quantitative conversions of the β-borated product were obtained within 6 hours (Table 3.7, entry 13). When the reaction was performed at lower reaction temperatures, a substantial decrease in the product formation was observed (Table 3.7, entries 14 and 15).

Table 3.7: Influence of iron on the catalytic β-boration of ethyl crotonate



Entry	Iron system	Cs_2CO_3 (mol %)	PPh_3 (mol %)	Temp(ºC)	Time(h)	Conv (%)
1	$Fe(acac)_2$	-	-	70	6	<5
2	$FeCl_2$	-	-	70	6	<5
4	$Fe(OMe)_2$	-	-	70	6	<5
5	$Fe(acac)_3$	-	-	70	6	<5
6	$Fe(acac)_2$	3	-	70	6/24	42/80
7	$FeCl_2$	3	-	70	6	60
8	$Fe(OMe)_2$	3	-	70	6	15
9	$Fe(acac)_3$	3	-	70	6	56
10	$Fe(acac)_2$	3	4	70	6/24	26/99
11	$Fe(acac)_2$	6	4	70	6	73
12	$Fe(acac)_2$	12	4	70	6	87
13	$Fe(acac)_2$	15	4	70	6	99
14	$Fe(acac)_2$	15	4	45	6	54
15	$Fe(acac)_2$	15	4	25	6	21

Standard conditions: ethyl crotonate / bis(pinacolato)diboron / Fe=0.5 mmol / 0.55 mmol / 0.01 mmol. Fe/PPh_3= 1:2, Cs_2CO_3: mol%, MeOH (100 μl, 5 eq.), solvent: THF (2mL). Conversion determined by GC

Although these preliminary results seemed very promising, recent evidences about the role of metal impurities in "iron-mediated" reactions[23] prompted us to carefully examine the possible effect of traces of transition metals in our iron precursors. As a matter of fact, the $Fe(acac)_2$ catalyst precursor received from Sigma–Aldrich (99.95%) reportedly contains copper and nickel impurities in 6.1 and 43.0 ppm concentrations, respectively. Phosphine complexes of copper and nickel are well-known catalysts for β-boration of activated olefins.[3d,4,5] No other metals, known to be active in β-boration of α,β-unsaturated carbonyl compounds, such as platinum, rhodium, and palladium were listed in the quality certificate of the iron source.

Under standard reaction conditions, the concentration of the iron was approximately $5\cdot10^{-3}$ M (Table 3.7, foot note). Considering the heavy metal impurities reported by the provider, the catalytic system might contain "in situ" formed copper/phosphine, nickel/ phosphine complexes in $1.2\cdot10^{-7}$ M and $9.2\cdot10^{-7}$ M concentrations, respectively. To estimate the contribution of the impurities to the overall catalytic activity, we monitored the conversion as the function of the phosphine-complex concentration for both copper and nickel. Since solutions of very low concentrations had to be prepared, we used stock solutions of Cu and Ni. $CuOTf\cdot4CH_3CN$ and $Ni(cod)_2$ were used instead of CuCl and $NiCl_2$ as a copper and nickel source due to their superior solubility in THF. For the same reason, NaOtBu was used as a base in the stock solutions because of its high solubility in tetrahydrofuran (Table 3.8, entry 1).

In subsequent experiments, always under standard reaction conditions (THF, 70ºC, 6h), we gradually decreased the concentration of the "in situ" formed, base-activated copper and nickel complexes. Both CuCl and $CuOTf\cdot4CH_3CN$ form considerably more active catalysts than $Fe(acac)_2$ when applied in the same concentration, $5\cdot10^{-3}$ M (Table 3.8, entries 2 and 3). The higher activity of copper is even more obvious when the catalyst concentration is decreased by one magnitude, to $5\cdot10^{-4}$ M (S/Cu=500), because the substrate is still quantitatively converted into the product.

Further decreasing the concentration of the copper complex, the conversion quickly diminishes. At $5\cdot10^{-5}$ M copper concentration only 5% of the product can be observed and at $5\cdot10^{-6}$ M concentration the substrate remains intact. (Table 3.8, entries 7 and 8).

Under the optimized conditions for Fe-mediated β-boration of ethyl crotonate, nickel complexes were much less active than the copper catalysts (Table 3.8, entries 9-11). Both $NiCl_2$ and $Ni(cod)_2$ provided moderate conversions when applied in the concentration of the iron precursor, and decreasing the nickel concentration by one magnitude resulted in complete inactivity.

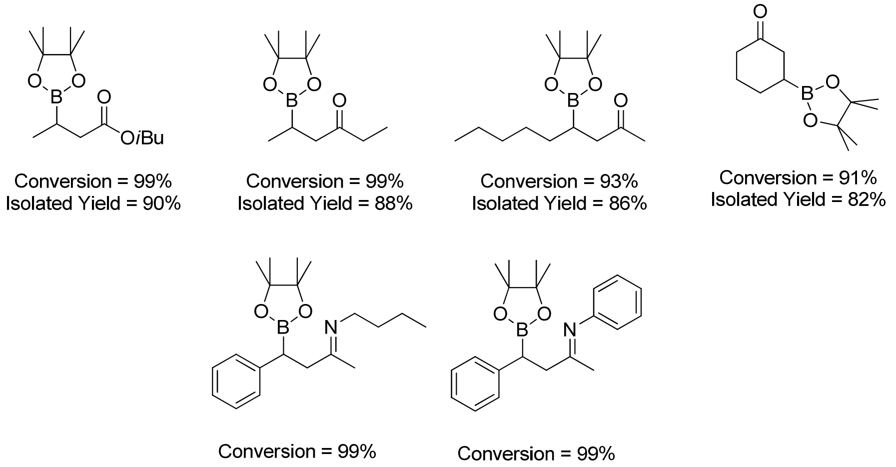
Table 3.8: Conversions in β-boration of ethylcrotonate with bis(pinacolato) diboron as the function of the concentration of copper and nickel, typical heavy metal impurities of the $Fe(acac)_2$ precursor

Entry	Precursor	Concentration (M)	Conv (%)
1	$Fe(acac)_2$	$5x10^{-3}$	45
2	CuCl	$5x10^{-3}$	99
3	$CuOTf{\cdot}4CH_3CN$	$5x10^{-3}$	99
4	$CuOTf{\cdot}4CH_3CN$	$5x10^{-4}$	99
5	$CuOTf{\cdot}4CH_3CN$	$2.5x10^{-4}$	28
6	$CuOTf{\cdot}4CH_3CN$	$1.25x10^{-4}$	17
7	$CuOTf{\cdot}4CH_3CN$	$5x10^{-5}$	5
8	$CuOTf{\cdot}4CH_3CN$	$5x10^{-6}$	0
9	$NiCl_2$	$5x10^{-3}$	53
10	$Ni(cod)_2$	$5x10^{-3}$	51
11	$Ni(cod)_2$	$5x10^{-4}$	0

Standard conditions: ethyl crotonate = 0.5 mmols, bis(pinacolato)diboron= 0.55 mmol; metal / PPh_3 / NaO*t*Bu=1 mmol / 2 mmol / 5 mmol; T=70ºC, t=6h, MeOH (100 μl, 5 eq.), solvent: THF (2 mL). Conversion determined by GC.

Considering the high purity of the $Fe(acac)_2$ precursor (99.95%), and the activity versus concentration profiles of the copper and nickel catalysts, it could be concluded that the heavy metal impurities could not contribute to the overall activity in the iron-mediated β-boration reactions.

Next, we became interested in increasing the substrate scope of the iron-mediated β-boration. Despite the steric hindrance of the isobutyl ester moiety, the $Fe(acac)_2/PPh_3/Cs_2CO_3$ system quantitatively converted isobutyl crotonate into the corresponding β-borated product under optimized conditions (Figure 3.2). The β-boration of acyclic and cyclic α,β-unsaturated ketones: *trans*-4-hexen-3-one, *trans*-3-nonen-2-one and cyclohexenone provided almost complete conversion towards the β-borated products (Figure 3.2). Remarkably, Ms. Cristina Sole, a members of our research group have also demonstrate that iron mediated the quantitive β-boration of 1-azadienes, such as (*E*)-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)aniline and (*E*)-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)butan-1-amine (Figure 3.2), which, to the best of our knowledge, have only been previously β-borated with copper.[24] Despite all our efforts, benzylidenacetone could not be β-borated with the iron catalytic system.



Conversion = 99%
Isolated Yield = 90%

Conversion = 99%
Isolated Yield = 88%

Conversion = 93%
Isolated Yield = 86%

Conversion = 91%
Isolated Yield = 82%

Conversion = 99%

Conversion = 99%

Figure 3.2: Influence of iron on catalytic β-boration of electron-deficient olefins with bis(pinacolato)diboron. (Standard conditions: Substrate / B_2pin_2 / $Fe(acac)_2$ / PPh_3 = 0.5 mmols / 0.55 mmols / 0.01 mmols / 0.02 mmols; Cs_2CO_3: 15 mol%, MeOH (100 μl, 5 eq.), solvent THF (2 mL), temperature 70ºC. Conversion determined by GC.

In order to gain deeper insight into the role of iron in the β-boration reactions, we have explored two possibilities: a) an iron complex activates the diboron reagent, thus forming Fe-B bonds (by oxidative addition[25] or transmetallation); b) the substrate is activated by the iron salt through a Lewis acid–base interaction between the metal and the carbonyl or imino group, polarizing the conjugated π-electron system of the substrate, and thus facilitating the boron-addition.

Towards this end, we first conducted $^{11}B\{^{1}H\}$ NMR studies with: a) 1 equivalent of $Fe(acac)_2$ and 1 equivalent of B_2pin_2 (Figure 3.3, left), b) 1 equivalent of $Fe(acac)_2$ + 1 equivalent of B_2pin_2 + 1 equivalent of NaOtBu (Figure 3.3, center) c) 1 equivalent of B_2pin_2 + 1 equivalent of NaOtBu (Figure 3.3, right). We observed that the diboron reagent was only affected by the base, independently of the presence or absence of $Fe(acac)_2$.

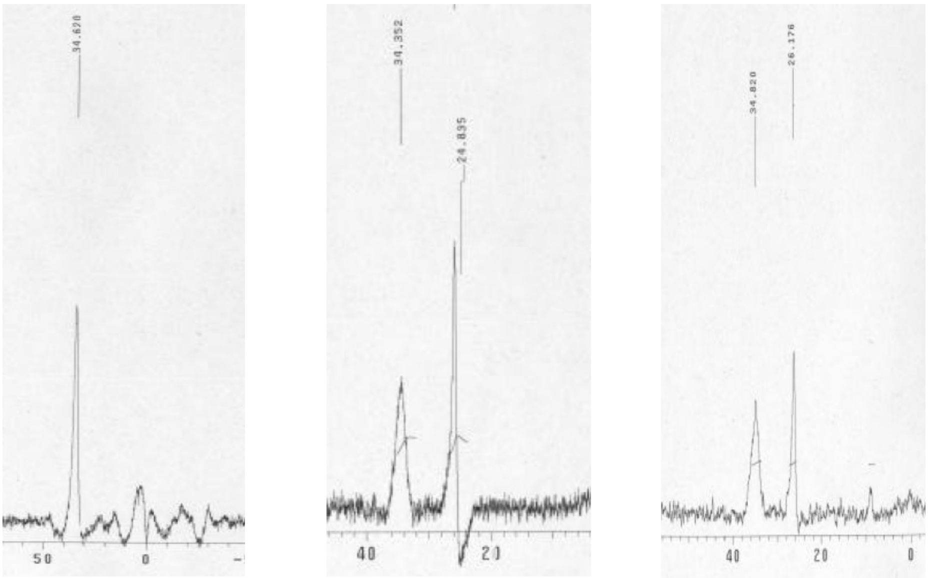


Figure 3.3: a) 1 equivalent of Fe(acac)$_2$ and 1 equivalent of B$_2$pin$_2$ (left); b) 1 equivalent of Fe(acac)$_2$, 1 equivalent of B$_2$pin$_2$, and 1 equivalent of NaOtBu (center); c) 1 equivalent of B$_2$pin$_2$ and 1 equivalent of NaOtBu (right)

In order to study possible interactions between the iron precursors and the substrates, we performed ESI-MS$^+$ analyses of solutions of Fe(acac)$_2$ in the presence of ethyl crotonate. The [Fe(acac)$_2$]/ethyl crotonate adducts was oxidized under the conditions of the ESI-MS$^+$ analysis and the molecular ion [Fe(acac)$_2$]$^+$-ethyl crotonate could be clearly observed. [Fe(acac)$_2$] and the corresponding adducts oxidized under the conditions of the ESI-MS$^+$ analysis.

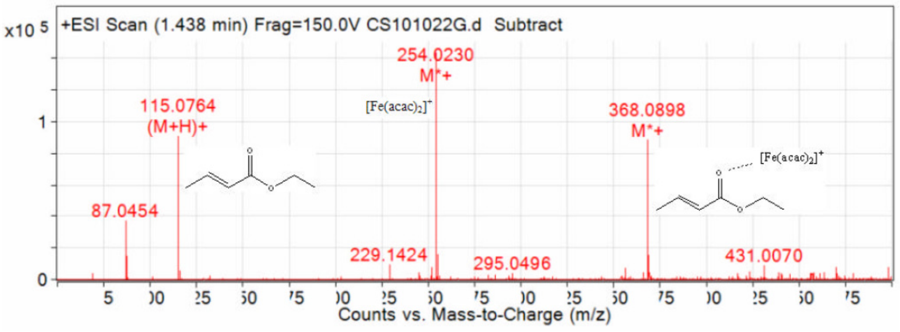
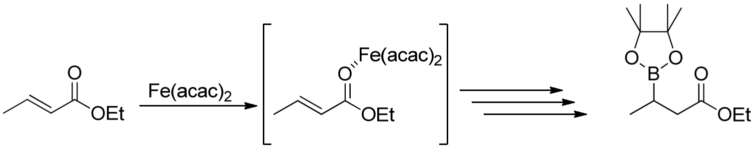


Figure 3.3: ESI-MS$^+$ analysis of Fe(acac)$_2$ and ethyl crotonate

It's important to note that the analogous [Fe(acac)$_2$]$^+$-chalcone adduct has been observed by ESI-MS in the FeCl$_3$/acac-catalyzed Friedel–Crafts alkylation of indoles.[26]

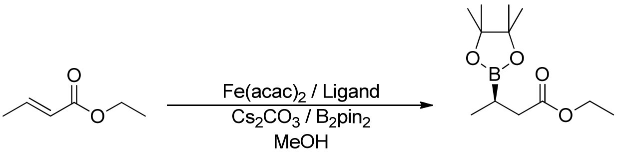
Based on these experimental results, we have suggesed a preactivation of the substrates by the Lewis acidic Fe(II) and Fe(III) salts (Scheme 3.11), as it has been proposed for the iron catalyzed Michael additions and other conjugate addition reactions.[27]

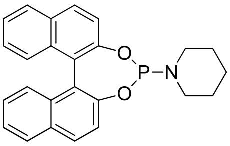


Scheme 3.11: Iron mediated β-boration reaction of activated olefins

We attempted to perform asymmetric iron assisted β-boration reaction under the optimized coniditons. Therefore, triphenylphosphine was replaced by chiral phosphorus ligands. Typical chiral ferrocenyl phosphine ligands that provide excellent enantioselectivities with Cu, Ni and Pd gave poor asymmetric inductions in the β-boration of ethyl crotonate assisted by Fe (Table 3.9). To our surprise, the monodentate phosphoramidites provided better enantioselectivities under optimized conditions, and these results improved when the reaction was performed at room temperature (Table 3.9). Decreasing the temperature of the reaction and/or the amount of base we observed a lower activity of the catalytic system, but a substantial increase in the enantioselectivity, obtaining enantioselectivities up to 63% (Table 3.9, entry 8).

Table 3.9: Enantioselective approach of iron assisted β-boration of ethyl crotonate





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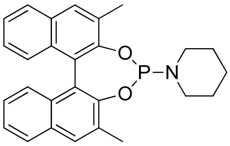

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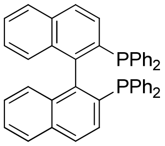
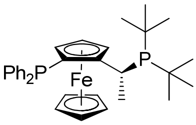
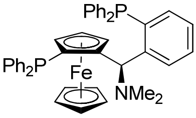


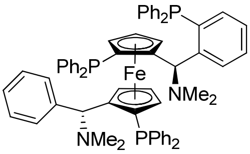
3.7



3.8



3.9



3.10

Entry	Iron system	Cs_2CO_3 (%)	Ligand	Temp(ºC)	Conv (%)	Ee (%)
1	Fe(acac)$_2$	15	3.5	70	54	26
2	Fe(acac)$_2$	15	3.6	70	94	35
3	Fe(acac)$_2$	15	3.7	70	63	<5
4	Fe(acac)$_2$	15	3.8	70	77	18
5	Fe(acac)$_2$	15	3.9	70	56	<5
6	Fe(acac)$_2$	15	3.10	70	72	<5
7[a]	Fe(acac)$_2$	3	3.8	70	70	36
8	Fe(acac)$_2$	15	3.6	25	42	63
9[a]	Fe(acac)$_2$	3	3.6	25	<5	-

Standard conditions: ethyl crotonate / bis(pinacolato)diboron / Fe = 0.5 mmols / 0.55 mmols / 0.01 mmols; Fe/Ligand= 1:2, Cs_2CO_3; MeOH (5 eq), Solvent: THF (2mL), Time: 6h, Conversion determined by GC. Enantioselectivy determinate by GC-Ms of the acylated product a) Time 24h

3.4 Analysis of the results and limitations

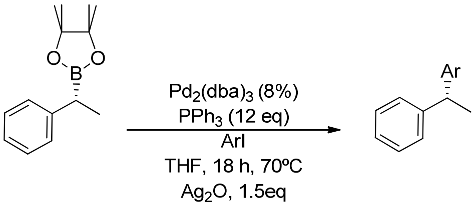
Palladium complexes have successfully been applied in β-boration reaction of a large scope of α,β-unsaturated esters, ketones, aldehydes and amides. We found it interesting that the same palladium catalytic system effectively catalyzed two consecutive reactions: β-boration of α,β unsaturated carbonyl compounds and cross coupling of the organoboronates with arylbromides. The two consecutive catalytic reactions were performed in one pot. However, this methodology could not be extended to the cross-coupling of internal β-boryl carbonyl compounds.

Iron salts facilitated the β-boration reaction but the iron system was less active than palladium, copper or nickel under the same reaction conditions. However the advantages of iron in terms of economy and environmental factors could compensate for the lower activity.

Despite the encouraging iron-assisted asymmetric approach in β-boration reaction (ee up to 63% with Fe / phosphoramidite ligand), there is a remaining important question to be answered. How the diboron reagent is activated in this reaction and how the pinacolboryl unit interacts with the α,β-unsaturated esters in an enantiodifferentiating fashion? To answer these questions we designed several reactions that opened up a new field of catalytic β-boration reaction, which we report in the following chapter.

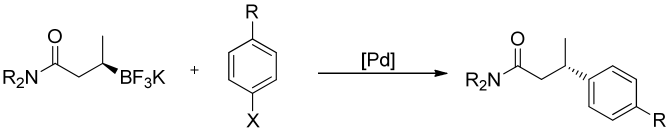
3.5 Current overview of Pd mediated cross-coupling of β-boryl carbonyl compounds after our contribution

Crudden and coworkers[28] reported the first example of the stereospecific coupling of acyclic chiral boronic esters with retention of the configuration in 2009 (Scheme 3.12). After that, Suginome and coworkers[29] have described a methodology that increased the substrate scope of chiral organoboron compounds containing α-amides, providing access to an important class of compounds.



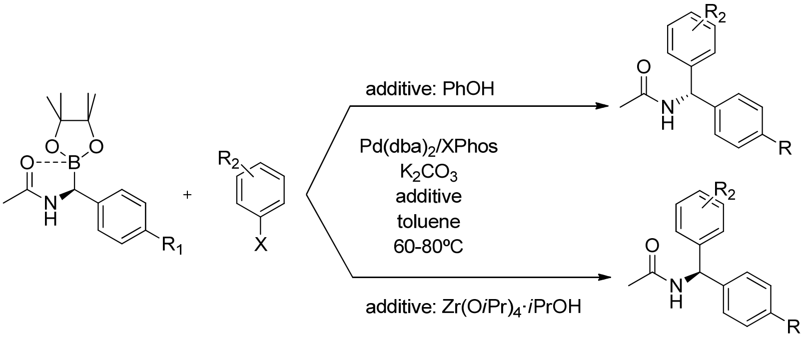
Scheme 3.12: General scheme of sp^2 cross-coupling with retention of configuration

In the course of the last years, chiral β-boryl carbonyl products have been proved to be challenging substrates for cross-coupling reactions. Molander and coworkers[30] reported a different methodology that involves trifluoroborate analogous providing the new C-R bond with inversion of configuration (Scheme 3.13).



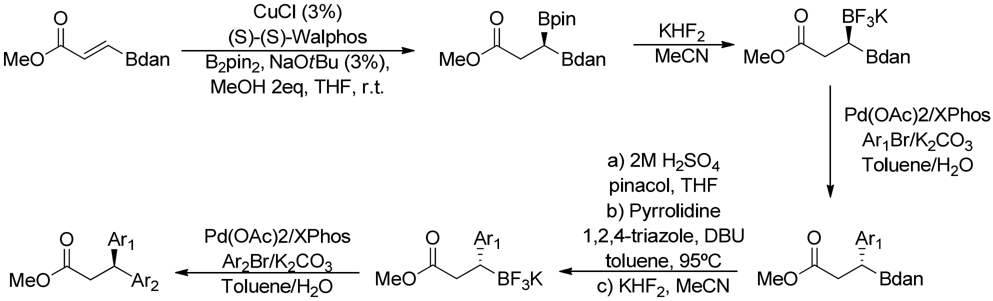
Scheme 3.13: General scheme of internal cross coupling with trifluoroborate salts

Recently, Suginome and coworkers[31], have progressed further, and described a stereospecific methodology that allowed to transform the C-Bpin bond into a new C-R bond with either retention or inversion of the configuration (Scheme 3.14).



Scheme 3.14: Representative reactions with retention or inversion of the new C-C bond

Recently, Hall and coworkers[32] developed a new methodology that involved a very elegant strategic synthetic route towards 3,3-diboronyl carboxyesters. This reaction has been designed based on the enantioselective nucleophilic addition of L*Cu-Bpin to the beta carbon of 1,8-diaminonaphtalenyl (dan) 3-boryl enolates (Scheme 3.15). The resulting enantioenriched 3,3-diboronyl carboxyesters have two different types of boryl units at the beta carbon, and can be cross-coupled chemoselectively and stereoselectively with several organic electrophiles.



Scheme 3.15: General scheme of cross coupling of 1,1-diboron compounds

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The man with a new idea is a crank until the idea succeeds.

Mark Twain

4 Organocatalytic β-boration of α,β-unsaturated carbonyl compounds

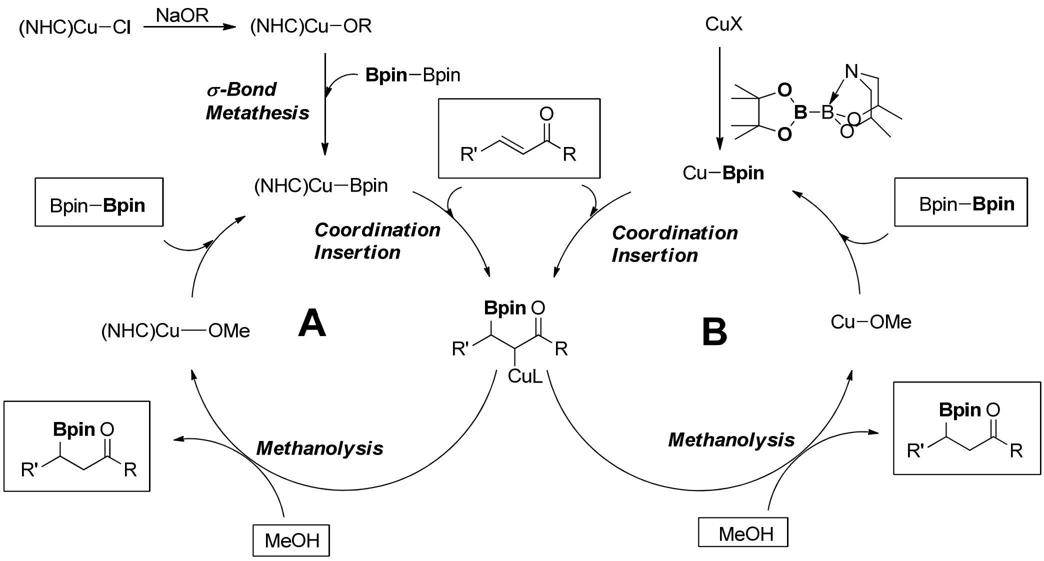
Table of contents

4.1 Introduction

Enantioenriched α-chiral organoboron compounds were first obtained from the catalytic hydroboration of prochiral alkenes using chiral rhodium–phosphine complexes as catalyst.[1] There are three reasons why metal-mediated asymmetric induction in C-B bond formation is more successful than existing methods involving interactions between the substrate and a chiral borane reagent[2] in the absence of a metal: 1) the low cost/availability of the achiral borane reagent, 2) the milder reaction conditions, and, most importantly, 3) the possibility of optimization and maximization of the asymmetric induction by screening the chiral ligands. Considerable progress has been made since then, particularly in relation to the enantioselective metal-mediated hydroboration,[3] diboration,[4] and β-boration[5] of electron-deficient olefins. However, one challenge still remains to be overcome: the development of a metal-free asymmetric boron-addition reaction with achiral boron reagents.

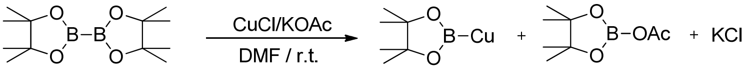
Our group has recently studied the metal-mediated conjugate borylation reactions, specially focused on the asymmetric version of the reaction, in the presence of copper,[5c,d] palladium,[5g] nickel,[5g] and iron complexes that were modified with either chiral phosphine or N-heterocyclic carbene ligands.

The presence of a base in the majority of these catalytic systems is essential,[6] but its role has not yet been elucidated completely. In metal-mediated β-boration of α,β-unsaturated carbonyl compounds, when the metal center does not activate the diboron by oxidative addition, the base has been used for in situ generation of metal alkoxide complexes, to facilitate σ-bond metathesis with diboron reagents[5,7] (Scheme 4.1, cycle A). This is consistent with the fact that isolated transition metal alkoxides, such as [(NHC)CuOR] (NHC=N-heterocyclic carbene; OR=OMe, O*t*Bu), can catalyze the reaction in the absence of base.[8] However, other exceptions to the required use of base in boron conjugated addition reactions[9] might suggest other important roles to be attributed to the base. For instance, Santos and coworkers have shown that the pinacolboryl unit of a mixed sp^2–sp^3 diboron reagent can selectively be added to the β-carbon atom of α,β-unsaturated carbonyl compounds and allenoates, by using phosphine free Cu(I) complexes as catalysts, in the absence of base (Scheme 4.1, cycle B).[10]



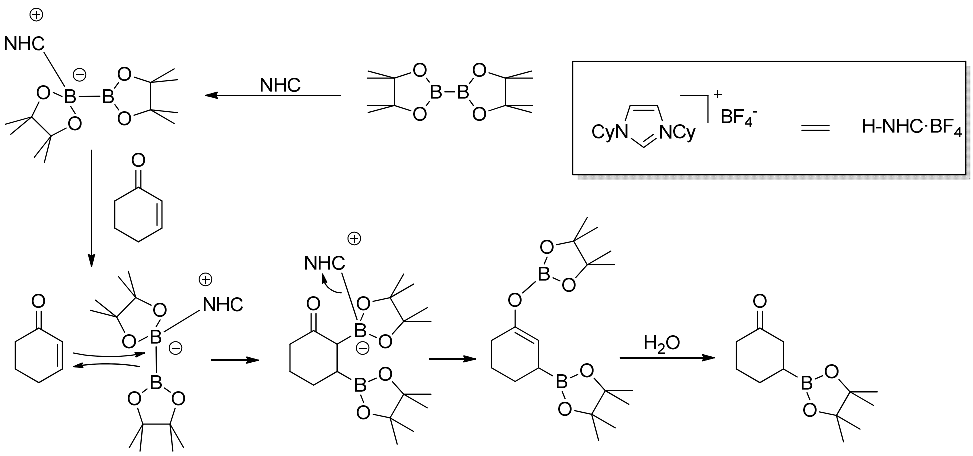
Scheme 4.1: Cycle A: Catalytic cycle where base promotes the σ-bond metathesis pathway; Cycle B: Catalytic cycle where the activation of the diboron reagent takes place intramolecularly

This "preactivated" diboron reagent was developed from the original idea of Miyaura and coworkers,[7b] who suggested that AcO$^-$ activated bis(pinacolato)diboron (B_2pin_2), by a Lewis acid–base interaction, prior to the boryl transfer to the copper center (Scheme 4.2).



Scheme 4.2: Bis(pinacolato)diboron activation suggested by Miyaura and coworkers

Hoveyda and coworkers have recently reported an efficient metal-free β-boration of cyclic and acyclic α,β-unsaturated carbonyl compounds promoted by N-heterocyclic carbenes (NHC-s).[11] (Scheme 4.3).



Scheme 4.3: Scheme of NHC mediated organocatalytic β-boration of a cyclic enone

In NHC-catalyzed reactions, the base was suggested to be used for in situ generation of the nucleophilic carbene by deprotonation of the corresponding imidazolium salt, and the carbene subsequently activates the diboron reagent through Lewis acid–base interaction.[11] By using a combination of 10 mol% of imidazolium salt and 10 mol% of NaO*t*Bu, cyclohexenone could be quantitatively converted to the corresponding β-borated product at room temperature.[11]

When we developed the iron assited β-boration reaction (*Chapter 3*), we observed that iron catalysts did not react with the diboron reagent, but instead of that, iron interacted with the substrate and this interaction activated the substrate and enhanced the speed of the boron conjugate addition reaction.

4.2 Work hypothesis

In the catalytic β-boration reaction, the boryl synthon is required to interact with the β-carbon of the α,β-unsaturated carbonyl compounds. So far, transition metal complexes have been required to activate the diborons by oxidative addition or σ-bond metathesis, and the presence of a base was essential in most of the cases.

If base assisted the heterolytic cleavage of diboron, is the metal required to catalyze the β-boration reaction of electron-deficient olefins?

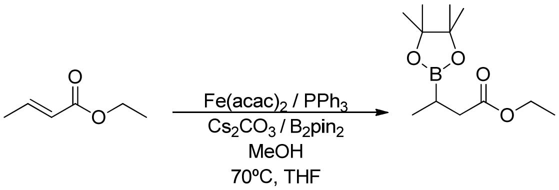
4.3 Results and discussion

When we explored the iron mediated β-boration reaction, we found that in the absence of base the iron salt $Fe(acac)_2$ did not convert the ethyl crotonate into the β-borated product. Similarly, the iron system $Fe(acac)_2/PPh_3$ was inactive, unless the base was present in the reaction mixture. A basic question araise at this point: is the base responsible for the catalytic β-boration of ethyl crotonate?

To answer this question we planned a blank experiment. Since total conversion into the β-borated product was obtained with 2% of $Fe(acac)_2$, 4 mol % of PPh_3, 5 equivalents of MeOH and 15 mol % of Cs_2CO_3 (Table 4.1, entry 1), we repeated the same reaction in the absence of iron. To our surprise, ethyl crotonate was β-borated up to 54% of conversion (Table 4.1, entry 2). From this experiment we understood that the iron center should be favouring the β-boration reaction, probably by interaction with the substrate as it was discussed in the previous chapter. However a new question was more intriguing at that moment. How important is the phosphine in the absence of the iron precursor? To answer this question we also performed the β-boration of ethyl crotonate with only cesium carbonate (15 mol %) and methanol (5 eq). Under these reaction conditions the β-borated product was obtained in 45 % of GC Yield (Table 4.1, entry 3).

From these experiments we concluded that the base and methanol were the real catalytic system, because in their absence, the substrate was almost unaltered (Table 4.1, entries 4 and 5).

Table 4.1: Blank experiments in iron mediated β-boration reaction

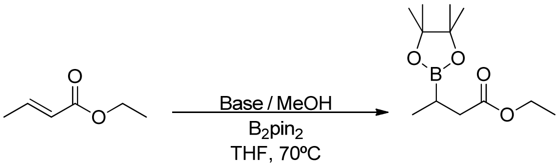


Entry	Iron system (%)	Ligand (%)	Base (%)	MeOH	Conv (%)
1	$Fe(acac)_2$ (2%)	PPh_3 (4%)	Cs_2CO_3 (15%)	5 eq	99
2	-	PPh_3 (4%)	Cs_2CO_3 (15%)	5 eq	54
3	-	-	Cs_2CO_3 (15%)	5 eq	45
4	-	PPh_3 (4%)	-	5 eq	1
5	-	PPh_3 (4%)	Cs_2CO_3 (15%)	-	12

Standard conditions: ethyl crotonate/bis(pinacolato)diboron = 0.5 mmols / 0.55 mmols; solvent: THF (2mL), time: 6h, temperature: 70ºC. Conversion determined by GC analysis.

Conceptually these set of experiments suggested a novel and fundamental role for the base. Could it be the catalyst? To learn more about the catalytic potential of the base in the β-boration of activated olefins, we conducted a systematic study to convert ethyl crotonate to the β-borated product in the presence of a series of bases. Methanol in the presence of metal alkoxides, metal carbonates and cesium fluoride allowed low to moderate conversion of the substrate at 70ºC in 6 h (Table 4.2).

Table 4.2: Base mediated β-boration of ethyl crotonate with B_2pin_2



Entry	Base	Alcohol	Solvent	Conv (%)
1	NaOMe	MeOH	THF	27
2	KOMe	MeOH	THF	24
3	LiOMe	MeOH	THF	23
4	NaO*t*Bu	MeOH	THF	40
5	Cs_2CO_3	MeOH	THF	45
6	K_2CO_3	MeOH	THF	28
7	CsF	MeOH	THF	29
8	Cs_2CO_3	MeOH	Toluene	33
9	Cs_2CO_3	BuOH	THF	41
10	Cs_2CO_3	*i*PrOH	THF	13
11	Cs_2CO_3	*t*BuOH	THF	8
12	Verkade's Base	MeOH	THF	69 (90)[a]

Standard conditions: ethyl crotonate (0.5 mmol), diboron reagent (B_2pin_2 1.1 eq.), base (15 mol%), alcohol (5 eq), solvent (2 mL), 70ºC, 6 h. Conversion calculated by GC analysis and confirmed by ^1H NMR spectroscopy. a) 16 h.

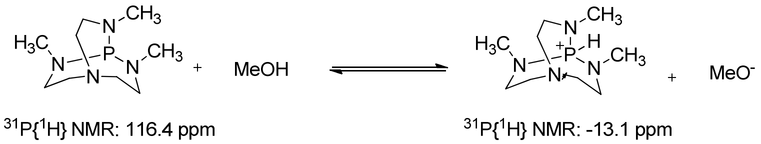
Mehoxide bases in combination with methanol allowed the β-boration of ethyl crotonate between 20-30% in 6h (Table 4.2, entries 1-3). Sodium *tert*-butoxide and cesium carbonate with methanol provided moderate conversions, between 40-45%, in 6h (Table 4.2, entries 4 and 5). Other carbonate salts and cesium fluoride, with methanol, diminished the rate of the reaction (Table 4.2, entries 6-7). We also studied the influence of solvents. THF provided better results than toluene, probably due to the higher solubility of the bases in polar solvents.

As far as the nature of the alcohol is concerned, primary alcohols (MeOH, BuOH) provided significantly higher conversions towards the β-borated product than secondary (*i*PrOH) and tertiary alcohols (*t*BuOH) (Table 4.2, entries 5, 9-11).

Verkade's base was the most active base providing 69% of conversion at 6h, and 90% when the reaction was carried out overnight (Table 4.2, entry 12).

$^{11}B\{^1H\}$ NMR experiments showed that the signals due to bis(pinacolato)diboron (30,5 ppm) did not change by the addition of Verkade's base in the absence of methanol.

$^{31}P\{^1H\}$ NMR studies showed that, when an excess of methanol was in the system, the Verkade base was totally protonated and, consequently, 1 equivalent of methoxide anion with respect to the amount of base was generated (Figure 4.1).



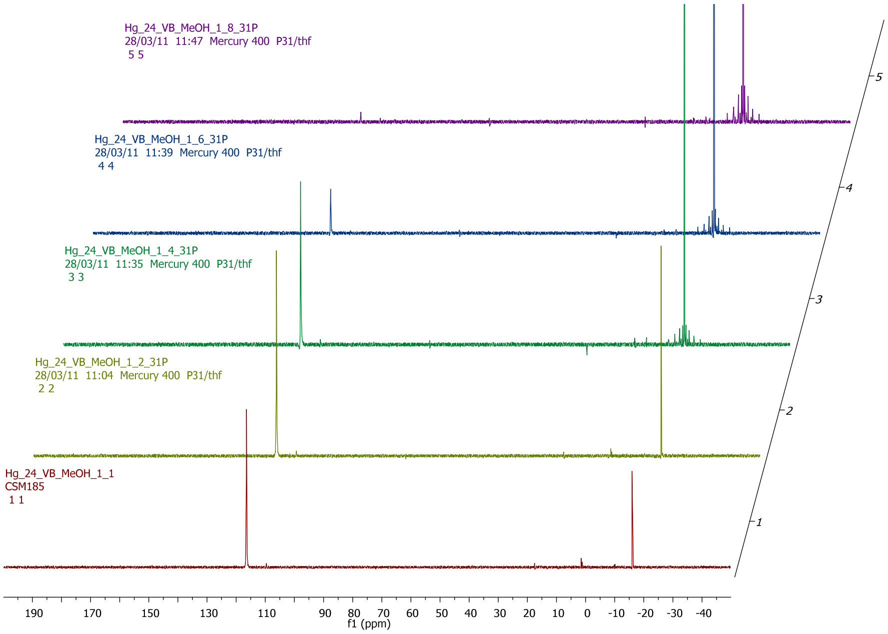


Figure 4.1: $^{31}P\{^1H\}$ NMR experiments mixing in THF the Verkade base / methanol. 1/1 red spectra, 1/2 ocher spectra, 1/4 green spectra, 1/6 blue spectra, 1/8 purple spectra

We also corroborated the existence of an acid-base equilibrium between the protonated Verkade and deuterated methanol (Figure 4.2).

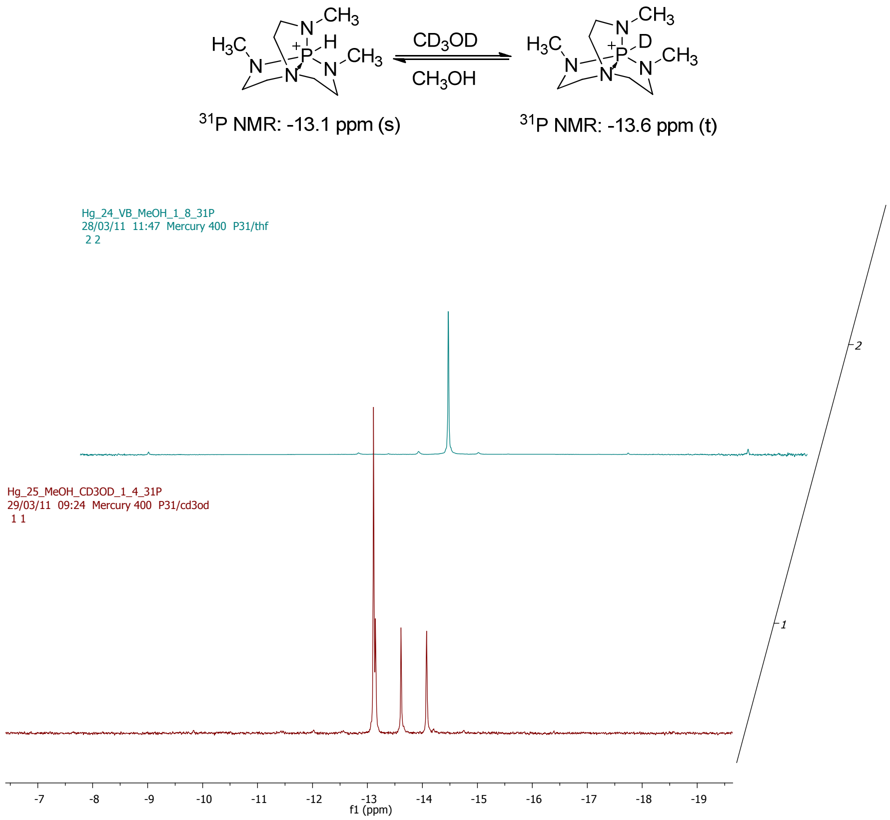


Figure 4.2: Blue spectra represents the Verkade base totally protonated. Red spectra shows a mixture between protonated Verkade base and partially deuterated Verkade base

Under argon, the Verkade base (1 mmol) and bis(pinacolato)diboron (0.5 mmol) were dissolved in THF (1 mL), and the solution was transferred into a quartz NMR tube, supplied with a capillary containing $Et_2O{\cdot}BF_3$, sealed with a rubber septum. $^{11}B\{^1H\}$ NMR spectrum of the solution displayed one intense signal at 30.8 ppm, discarding any interaction between the base and the B_2pin_2, also $^{31}P\{^1H\}$ NMR was intact. MeOH (0.5 mmol) was added to the solution via the septum. The $^{31}P\{^1H\}$ NMR spectrum of the solution showed that 46% of the Verkade base became protonated upon the interaction with the MeOH, in the presence of B_2pin_2. Considering the Verkade base / MeOH molar ratio, over 90% of the MeOH became deprotonated. In the $^{11}B\{^{1}H\}$ NMR, the original signal of B_2pin_2 (30.5 ppm) was splitted in two new signals: A broad signal at 42 ppm and a less broad signal at 5.9 ppm (Figure 4.3). The new resonances were attributed to the formation of the [MeO→Bpin-Bpin]$^-$ adduct and the broadness of the signals are probably due to the fast inter- and intramolecular exchanges.[12] The new signal that appeared at higher chemical shifts has been related to the sp^2 boryl unit and the new signal at lower chemical shift was assigned to the sp^3 boryl unit. Therefore the activation of the bis(pinacolato)diboron by the base, methanol was conclusive at that point, providing two different environments for the diboron reagent. The [MeO→Bpin-Bpin]$^-$ adduct was postulated and it could be observed by ESI-MS experiments.

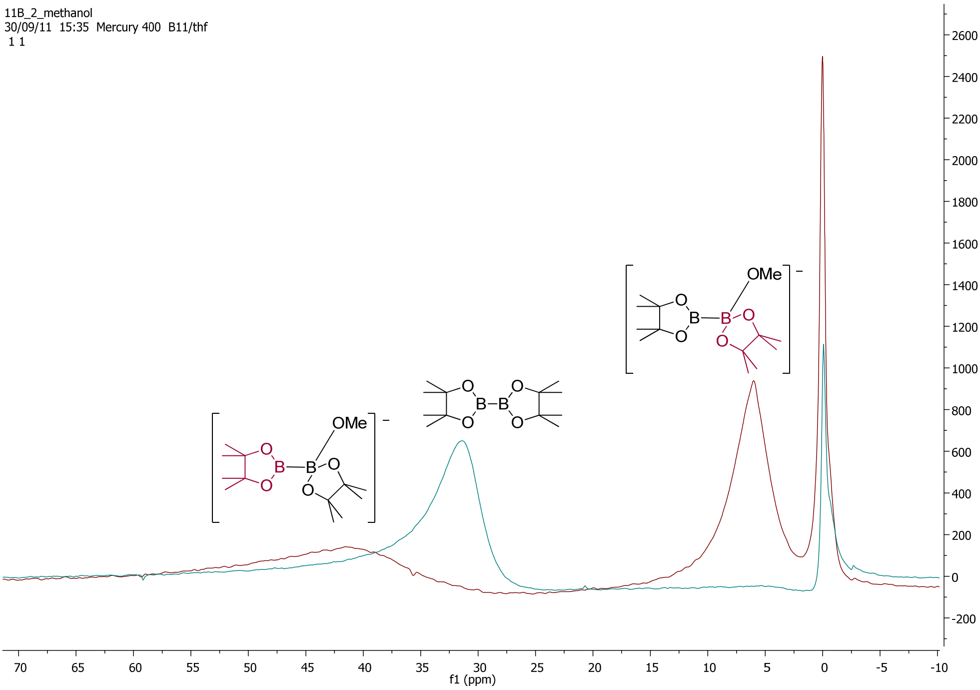
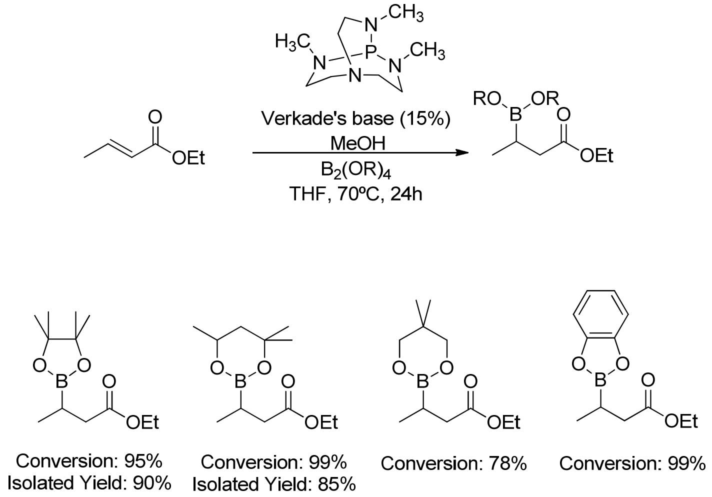


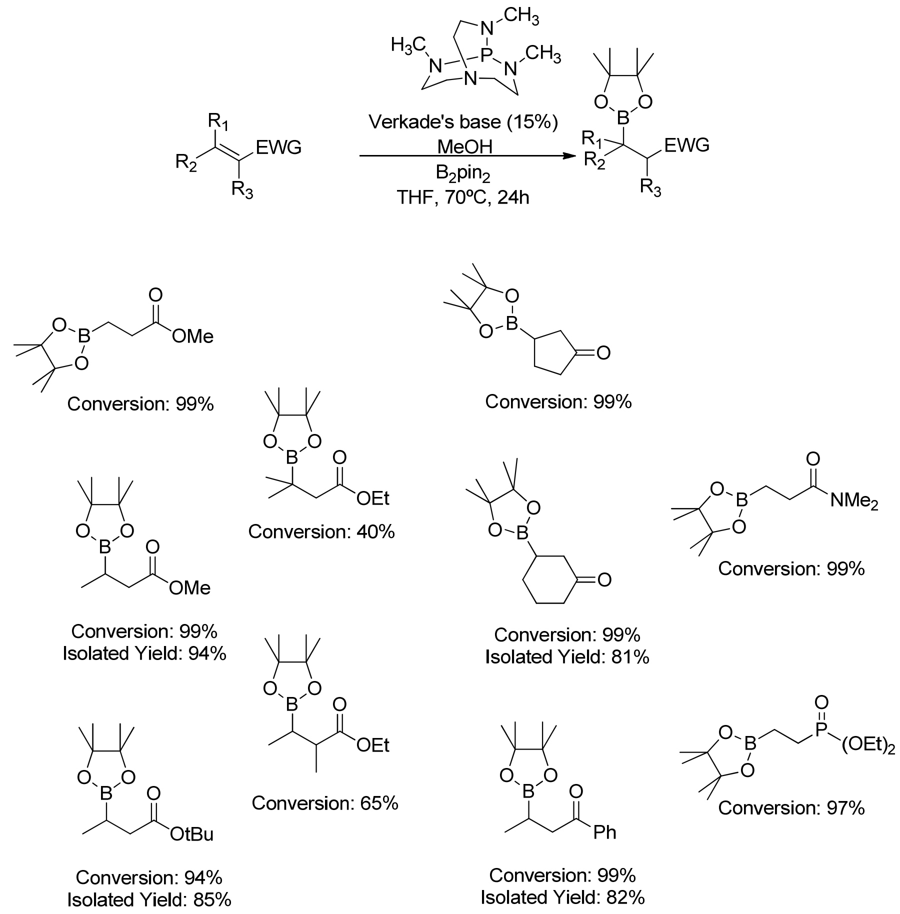
Figure 4.3: Blue spectra: $^{11}B\ \{^{1}H\}$NMR of B_2pin_2. Red spectra: ^{11}B NMR of the adduct [MeO→Bpin-Bpin]$^-$, $\delta Bsp^2 = 39.7$ ppm, $\delta Bsp^3 = 5.9$ ppm. Internal standard: $BF_3{\cdot}Et_2O$

The fact that bis(pinacolato)diboron interacted with the methoxi anion to promote the heterolytic cleavage of B-B bond of the postulated adduct [MeO→Bpin-Bpin]$^-$, prompted us to search new potential diboron-OMe$^-$ adducts. Towards this end we selected the most common and commercially available diboron reagents in order to compare their reactivity. Pleasantly, all the diboron reagents could be activated with this method. In most of the cases total conversion was obtained after 24 hours of reaction time, only bis(neopentylglycolato)diboron did not provide total conversion towards the β-borated product (Scheme 4.4).



Scheme 4.4: Verkade/MeOH mediated β-boration of ethyl crotonate with different diboron reagents. Standard conditions: substrate (0.5 mmol), diboron reagent ($B_2(OR)_4$ 1.1 eq.), base (15 mol%), alcohol (5 eq.), solvent (2 mL), 70ºC, 24 h

At this point, we wanted to extend the substrate scope to other α,β-unsaturated compounds. Under optimized reaction conditions, the α,β-unsaturated esters were quantitatively β-borated regardless of the steric bulk of the ester moiety. However α,β–unsaturated esters with subtituents on α and β positions diminished the rate of the reaction due to steric factors. Cyclic and acyclic ketones were quantitatively converted to the corresponding organoboranes. α,β-Unsaturated amides and phosphonates could be conveniently converted into the desired product within 24h. (Scheme 4.5).



Scheme 4.5: Substrate scope of the Verdake/MeOH mediated β-boration reaction. Standard conditions: substrate (0.5 mmol), diboron reagent (B_2pin_2 1.1 equiv), base (15 mol%), alcohol (5 eq), solvent (2 mL), 70ºC, 24 h

To gain more insight into the mechanism of the base/MeOH catalyzed β-boration reaction, a series of theoretical calculations were carried out by Ms Cristina Pubill-Ulldemolins under the supervision of Dr. Carles Bo (ICIQ) within the framework of a cosupervised thesis with Dr. Elena Fernández. The theoretical calculations confirmed that the methoxide anion, generated from the MeOH in the presence of base, forms a Lewis acid-base adduct with bis(pinacolato)diboron (Figure 4.4).

According to the DFT calculations, the sp^2 moiety of the Lewis acid-base adduct had an increased negative charge with respect to the boryl moiety of bis(pinacolato)diboron. The sp^2 boron moiety has higher electron density due to the electron density transfer from the sp^3 moiety. The net result is that in [MeO→Bpin-Bpin]$^-$, the B-B σ-bond became polarized and the sp^2 boron atom gains a strong nucleophilic character.

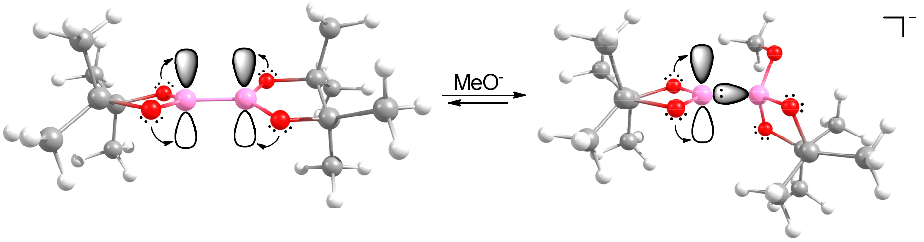
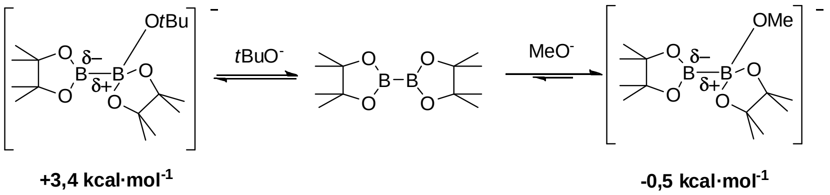


Figure 4.4: [MeO→Bpin-Bpin]$^-$ formation and consequent polarization of the B-B bond

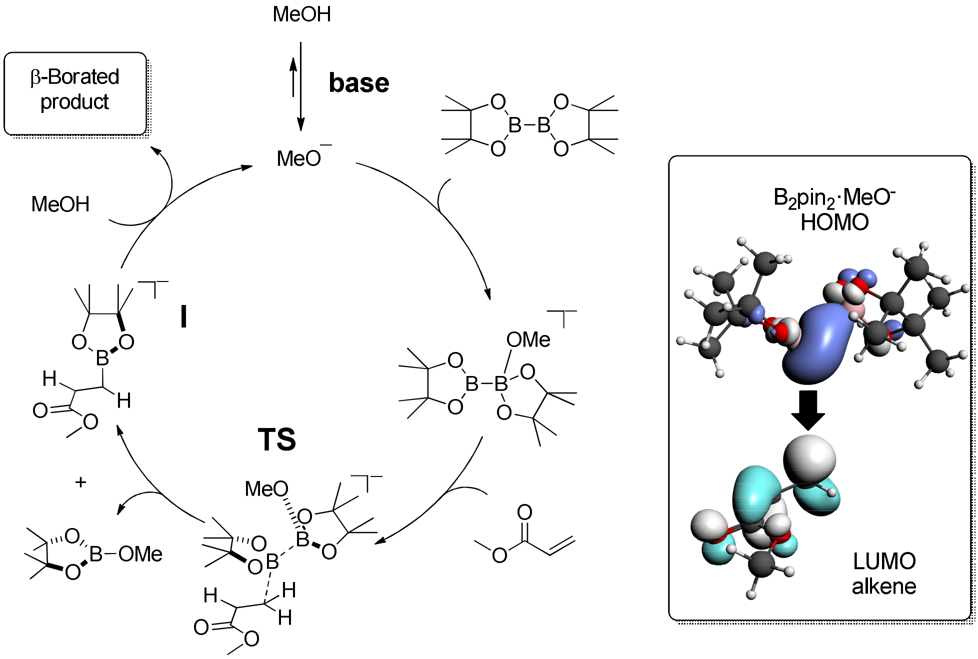
Next, the influence of the nature of the alcohol was studied in the interaction with B_2pin_2 (Scheme 4.6). The dramatic decrease in activity when *t*BuOH was used instead of MeOH (Table 4.2, entries 5 and 11, conversion with methanol 45%, conversion with *tert*-butanol 8%) could be explained by two factors: 1) *t*BuOH is less acidic than MeOH, and therefore, the generation of the alkoxide could be less favored; 2) the alkoxide-diboron adducts seems to be thermodynamically favored in the case of the [MeO→Bpin-Bpin]$^-$ (-0,5 kcal·mol^{-1}) versus the [*t*BuO→Bpin-Bpin]$^-$ (+3,4 kcal·mol^{-1}).



Scheme 4.6: Energies for the formation of the Lewis acid-base adduct with methoxide and *tert*-butoxide, supplied by Ms. C. Pubill-Ulldemolins and Dr. C. Bo

A catalytic cycle has been postulated based on the theoretical calculations of Ms. C. Pubill-Ulldemolins and Dr. C. Bo. The [MeO→Bpin-Bpin]$^-$ adduct has been selected as the origin of energies and methyl acrylate has been chosen as model substrate. The catalytic cycle starts with the formation of the adduct [MeO→Bpin-Bpin]$^-$ from the methoxide (generated with the base and methanol) and the diboron reagent (Scheme 4.7). A transition state

(TS) has been found and fully characterized as the nucleophilic attack of the sp^2 boron moiety of the adduct at the β-carbon atom of the activated alkene. This interaction has been identified as the overlap between the strongly polarized B-B σ orbital (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the alkene. The heterolytic cleavage of the B-B bond leads to the negatively charged intermediate I, and the byproduct MeOBpin. The intermediate I suffered protonation and forming the β-borated product and the generating another methoxide anion that regenerate the catalytic cycle (Scheme 4.7).



Scheme 4.7: Catalytic cycle of organocatalytic β-boration of α,β-unsaturated carbonyl compounds based on theoretical calculations

It has also found that there are small but informative difference between the energy profiles relative to the [MeO→Bpin-Bpin]$^-$ and the corresponding α,β-unsaturated aldehydes, ketones and esters, being the aldehyde the most reactive and the ester the less reactive (Figure 4.5).

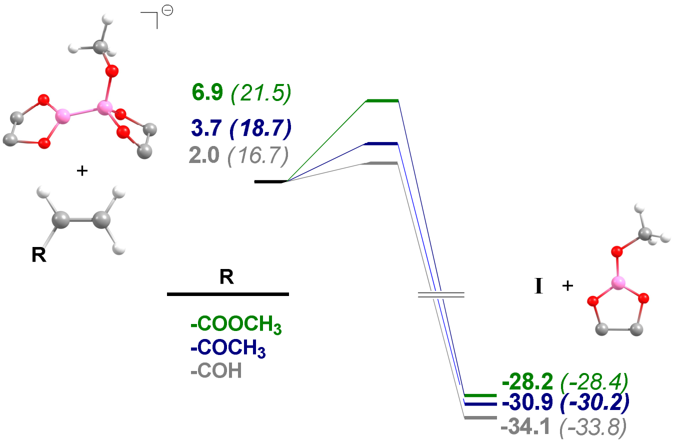
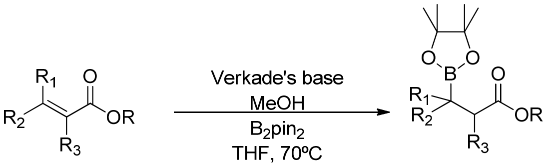
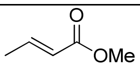
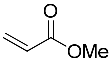
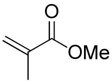
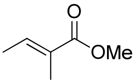
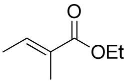
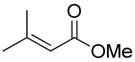


Figure 4.5: Energy profile for the β-boration of different α,β-unsaturated carbonyl compounds (methyl acrylate, methyl vinyl ketone and acrolein). Energy barriers and reaction energies are given as electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level relative to [MeO→Bpin-Bpin]$^-$ adduct plus the respective alkene. All values in kcal·mol^{-1}. All this data was calculated by Ms. C. Pubill-Ulldemolins and Dr. C. Bo

Considering the α,β-unsaturated esters as model substrates, Ms C. Pubill-Ulldemolins and Dr. C. Bo also observed that the energy barrier significantly increased when there were methyl groups in the β-position (Table 4.3, entries 1, 2 and 6) in agreement with the lower conversion observed in the corresponding experiments. The influence of a methyl group in α position was not as pronounced as in β-position (Table 4.3, entries 1, 5 and 2, 3). Also the replacement of the methyl group by an ethyl group in the ester moiety did not affect to the energy barrier and justifying the similar reactivities observed experimentally.

Table 4.3: Relative energies ($\Delta E^{\ddagger}$) (kcal·mol^{-1}) in the activation of substituted α,β-unsaturated esters, compared with the model substrate (methyl crotonate) calculated by Ms. C. Pubill-Ulldemolins and Dr. C. Bo



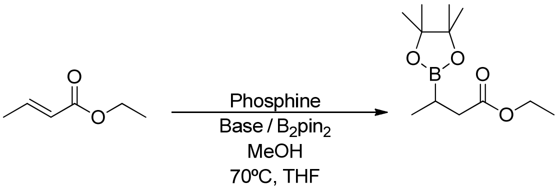
Entry	**Substrate**	**Conversion**	**ΔE^{+}**	**$\Delta E_{ENTRY1}^{\ddagger}$-$\Delta E^{\ddagger}$ (kcal·mol^{-1})**
1		99	14.0	**0**
2		99	6.9	**-7.1**
3		-	10.2	**-3.8**
4		-	16.3	**+2.3**
5		65	17.1	**+3.1**
6		-	23.0	**+9.0**

Molecular geometries for all the species were optimized with BP86 functional. Single-point energies at the metahybrid M06 level are in parentheses. Standard conditions: substrate (0.5 mmol), diboron reagent (B_2pin_2 1.1 eq.), base (15 mol%), alcohol (2.5 mmol), solvent (2 mL), 70ºC, 24 h. Conversion calculated by GC analysis and confirmed by ^{1}H NMR spectroscopy.

Another interesting question arises from the blank experiments shown in the Table 4.1: What is the role of the phosphine in the organocatalytic β-boration reaction? It seems to enchance the reaction rate (Table 4.1, entries 2-3), we explored the synergic effect of the phosphine in the organocatalytic β-boration of ethyl crotonate. The nature of the phosphine could be expected to be important. Hoveyda and coworkers[11] found that O=PPh$_3$ promoted the β-boration of 2-cyclohexene-1-one with moderate conversion, even in the absence of base. Under our reaction conditions , the use of triphenylphosphine oxide provided much lower activity than triphenylphosphine (Table 4.4, entry 4). The use of diphosphines, 1,2-

bis(di-tert-butylphosphinomethyl)benzene (DTBPMB) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) provided moderate conversions towards the β-borated product (Table 4.4, entries 5 and 6). The use of tricyclohexylphosphine performed a more active catalytic system and favors the quantitative conversion in 6h with only 4% of phosphine loading (Table 4.4, entry 9) comparable to the use of 20% of PPh_3 (Table 4.4, entry 8). Despite the obvious importance of the structure of the phosphine, the nature of the base and alcohol was found to be the most important factor. Changing from MeOH to *i*PrOH and cesium carbonate to sodium methoxide or sodium acetate, the formation of the β-borated product was less favoured (Table 4.4, entries 3 and 9-11).

Table 4.4: Cooperative effect of phosphines in the organocatalytic β-boration of ethyl crotonate



Entry	Ligand (mol %)	Base (mol %)	Alcohol	Conv (%)
1	-	Cs_2CO_3	MeOH	45
2	PPh_3 (4%)	Cs_2CO_3	MeOH	54
3	PPh_3 (4%)	Cs_2CO_3	*i*PrOH	49
4	(O)PPh_3 (4%)	Cs_2CO_3	MeOH	21
5	DTBPMB (4%)	Cs_2CO_3	MeOH	32
6	DPPF (4%)	Cs_2CO_3	MeOH	39
7	PPh_3 (10%)	Cs_2CO_3	MeOH	63
8	PPh_3 (20%)	Cs_2CO_3	MeOH	99
9	PCy_3 (4%)	Cs_2CO_3	MeOH	99
10	PCy_3 (4%)	NaOMe	MeOH	55
11	PCy_3(4%)	NaOAc	MeOH	7

Standard conditions: ethyl crotonate / bis(pinacolato)diboron = 0.5 mmols / 0.55 mmols; Phosphine (mol %), Cs_2CO_3: (15 mol %), alcohol (5 eq.), solvent: THF (2mL), 70ºC, 6h. Conversion determined by GC analysis.

The substrate scope of the organocatalytic β-boration reaction was studied using the optimized conditions and triphenylphosphine. The structure-activity relationships in the β-boration of α,β-unsaturated esters showed certain trends (Figure 4.6). Higher conversion was observed when the ester moiety was less sterically hindered. Also, α and β substituents in the ester decrease significantly the conversion. The α,β-unsaturated ketones were less sensitive to structural changes and they were readily converted into the corresponding β-boryl ketones. On the other hand, cyclic ketones showed lower activity than the acyclic analogues. Also, phenyl substituent on the β-carbon diminished the reaction rate dramatically, for instance, <5% of conversion was observed in the case of benzilideneacetone.

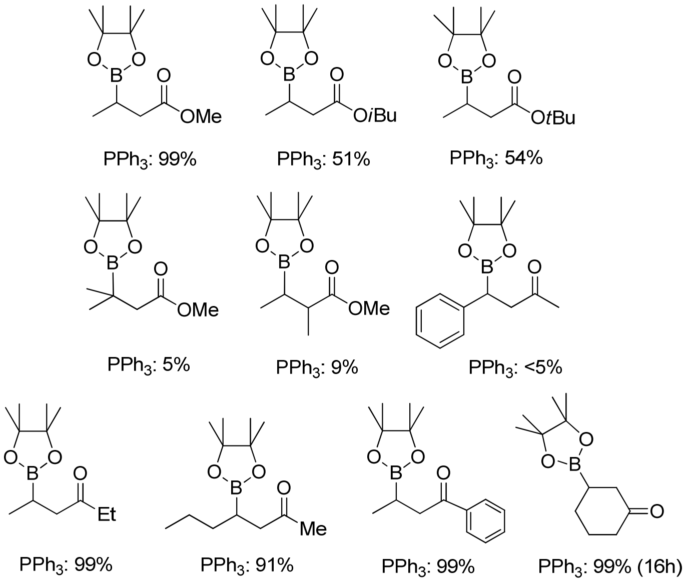
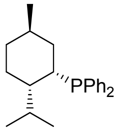


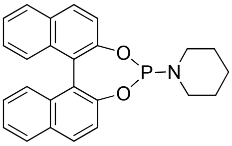
Figure 4.6: Scope of organocatalytic β-boration reaction. Standard conditions: ethyl crotonate / bis(pinacolato)diboron = 0.5 mmols / 0.55 mmols; Phosphine (mol %), Cs_2CO_3: (mol %), alcohol (5 eq.), solvent: THF (2mL), 70ºC, 6h

Having identified the appropriate reaction conditions and knowing that the methodology could be extended to other substrates, we focused our efforts on obtaining asymmetric induction in the model reaction. Chiral monophosphorous compounds, as well as diphosphines, were explored as chiral auxiliaries of the reaction, at 4 mol % loading, in the β-boration of ethyl crotonate. The fairly basic (+)-neomenthyldiphenylphosphine (**4.1**) provided good conversion, but no asymmetric induction (Table 4.5, entry 1). Chiral monodentate phosphoramidites have also been tested (**4.2**-**4.4**) and, to our delight, they induced a certain degree of enantioselectivity (Table 4.5, entries 2-4). Importantly, the ee values were higher than the enantioselectivities achieved with the copper / binol phosphoramidite system reported by Yun and coworkers (<7% ee).[5a] Subsequently, bidentate phosphines (R)-3,5-Bu-4-MeO-MeOBiphep (**4.5**) and (R)-BINAP (**4.6**) were tested in the model reaction. Whereas MeOBiphep was a rather poor chiral auxiliary, BINAP provided quantitative conversions and 77% of enantiomeric excess (Table 4.5, entries 5 and 6). Bearing in mind the success of diphosphines containing a ferrocene moiety in their backbone in metal-mediated β-boration reactions,[5a] we focused our efforts on exploring chiral ferrocenyl diphosphines. When (R)-(S)-NMe_2-PPh_2-Mandyphos (**4.7**), (R)-(R)-Walphos-type diphosphine (**4.8**) and (R)-(S)-Taniaphos type diphosphine (**4.9**) were used in the β-boration of ethyl crotonate, comparable activities were observed but only **4.9** (Table 4.5, entry 9) induced notable stereoselectivity (72% of ee). Interestingly, all (R)-(S)-Josiphos type phosphines (**4.10**, **4.11** and **4.12**) provided much higher activities, but the asymmetric induction was very sensitive to the structure of the substituents of the phosphorous donor atoms (Table 4.5, entries 10-12). Under the applied conditions, diphosphine **4.12** was capable of inducing enantioselectivities up to 88%.

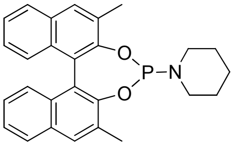
Table 4.5: Chiral-phosphines as chiral auxiliaries in the organocatalytic β-boration of ethyl crotonate with B_2pin_2



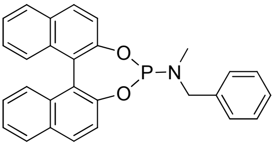
4.1



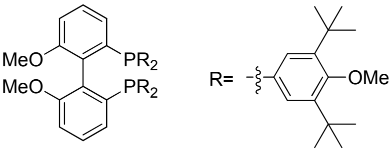
4.2



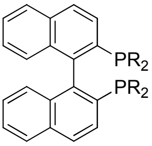
4.3



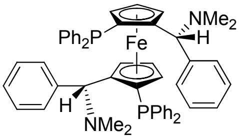
4.4



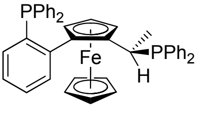
4.5



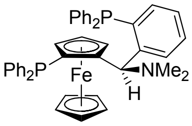
4.6



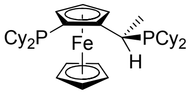
4.7



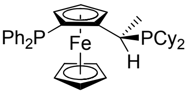
4.8



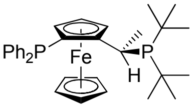
4.9



4.10



4.11



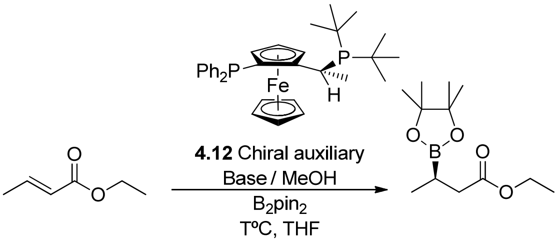
4.12

Entry	Chiral Auxiliary Component	Conversion (mol %)	Enantioselectivity (%)
1	(**4.1**)	74	<5
2	(**4.2**)	53	7 (R)
3	(**4.3**)	54	35 (S)
4	(**4.4**)	64	31 (S)
5	(**4.5**)	32	3 (S)
6	(**4.6**)	99	77 (S)
7	(**4.7**)	58	<5
8	(**4.8**)	54	23 (R)
9	(**4.9**)	64	72 (S)
10	(**4.10**)	89	25 (S)
11	(**4.11**)	99	75 (S)
12	(**4.12**)	94	88 (S)

Standard conditions: ethyl crotonate/bis(pinacolato)diboron = 0.5 mmol / 0.55 mmol; Chiral auxiliary component (4 mol %), Cs_2CO_3: (15 mol %), MeOH (5 eq.), solvent: THF (2ml). Conversion determined by GC

Performing the reactions at room temperature, a slight increase in the ee value (90%) was observed, but the activity decreased substantially (Table 4.6, entries 1 and 2). Interestingly, upon applying a smaller amount of base, the enantiomeric excess increased to 93% even at 70ºC, however, the lower amount of base decreased the catalytic activity, and therefore, in this case the reaction required 24h to reach a notable conversion (Table 4.6, entry 3). The combination of the chiral auxiliary **4.12** with other bases resulted in a less efficient systems, but in the case of CsF the stereoselectivity could be maintained (Table 4.6, entry 5). Finally, we became interested in comparing the asymmetric induction in the organocatalytic β-boration with the corresponding metal mediated β-boration reaction. Towards this end, we performed two catalytic reactions with CuCl and $NiCl_2$ modified with **4.12** as chiral ligand (Table 4.6, entries 6 and 7). Both metal catalyst provided relatively high activities, but the enantioselectivies were only moderate.

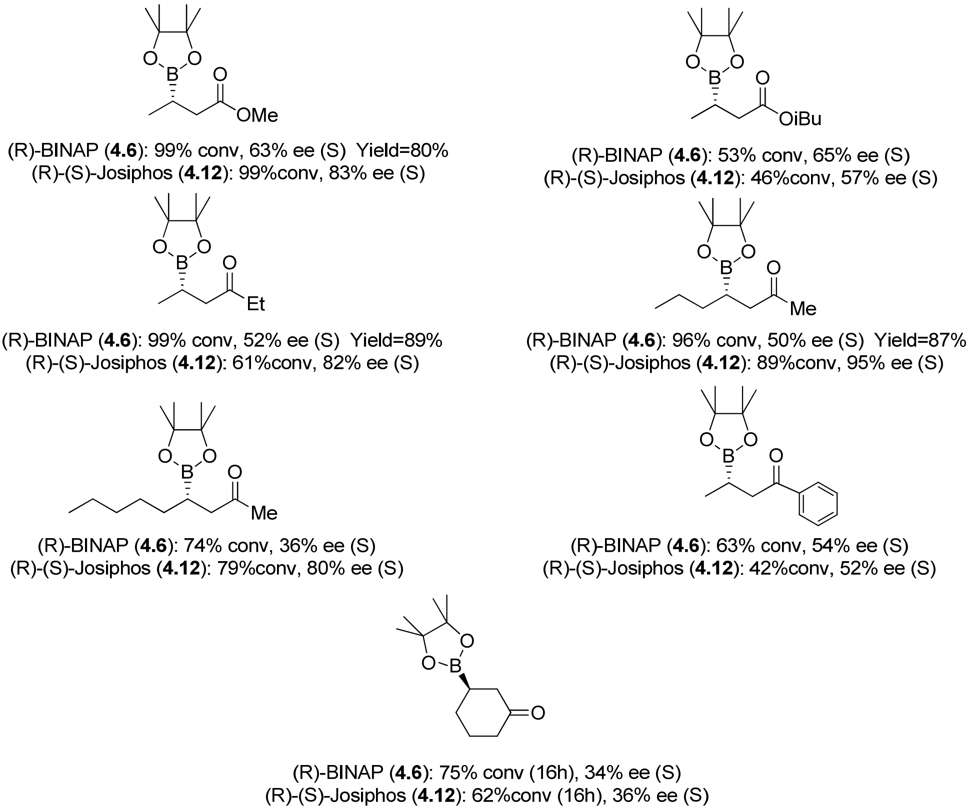
Table 4.6: Influence of chiral auxiliary **4.12** in the catalytic β-boration of ethyl crotonate with B_2pin_2



Entry	Chiral system	Base (%)	Temp (ºC)	Time (h)	Conv (%)	Ee (%)
1	**4.12**	Cs_2CO_3 (15%)	70	6	94	88 (S)
2	**4.12**	Cs_2CO_3 (15%)	25	6	17	90 (S)
3	**4.12**	Cs_2CO_3 (3%)	70	24	77	93 (S)
4	**4.12**	NaO*t*Bu (15%)	70	6	59	55 (S)
5	**4.12**	CsF (15%)	70	6	72	89 (S)
6[a]	CuCl/**4.12**	Cs_2CO_3 (15%)	70	6	97	54 (S)
7[a]	$NiCl_2$/**4.12**	Cs_2CO_3 (15%)	70	6	78	58 (S)

Standard conditions: ethyl crotonate/bis(pinacolato)diboron =0.5 mmol / 0.55 mmol, Chiral auxiliary (4 mol %), Base (mol %), MeOH (5 eq); Solvent: THF (2mL). Conversion determined by GC analysis. a) M / L = 1 / 1

We selected the best performing chiral auxiliaries (**4.6** and **4.12**) to study the substrate scope in the asymmetric β-boration of α,β-unsaturated carbonyl compounds under the optimized reaction conditions. The same trend that we observed with triphenylphosphine, was reproduced with the chiral phosphines: sterically demanding α,β-unsaturated esters were less efficiently transformed into the β-borated product (Figure 4.7). Conversion and stereoselectivity decreased when isobutyl crotonate was used as substrate. In contrast, the less bulky methyl ester substrate could be readily converted into the product. The enantioselectivities were comparable to the values observed with the model substrate. The organocatalysts were also very active for the transformation of acyclic and cyclic α,β–unsaturated ketones and we were pleased to see that the Josiphos type phosphine **4.12** assisted the β-boration of 3-heptene-2-one with 95% enantioselectivity. Lower selectivities were achieved in the β-boration of 2-cyclehexene-1-one and 1-phenyl-2-butene-1-one.



(R)-BINAP (**4.6**): 99% conv, 63% ee (S) Yield=80%
(R)-(S)-Josiphos (**4.12**): 99%conv, 83% ee (S)

(R)-BINAP (**4.6**): 53% conv, 65% ee (S)
(R)-(S)-Josiphos (**4.12**): 46%conv, 57% ee (S)

(R)-BINAP (**4.6**): 99% conv, 52% ee (S) Yield=89%
(R)-(S)-Josiphos (**4.12**): 61%conv, 82% ee (S)

(R)-BINAP (**4.6**): 96% conv, 50% ee (S) Yield=87%
(R)-(S)-Josiphos (**4.12**): 89%conv, 95% ee (S)

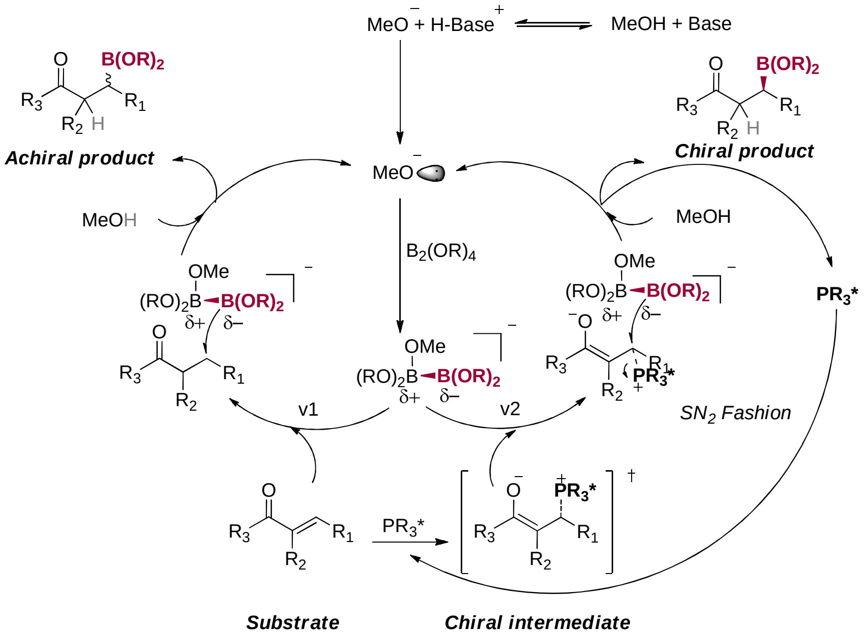
(R)-BINAP (**4.6**): 74% conv, 36% ee (S)
(R)-(S)-Josiphos (**4.12**): 79%conv, 80% ee (S)

(R)-BINAP (**4.6**): 63% conv, 54% ee (S)
(R)-(S)-Josiphos (**4.12**): 42%conv, 52% ee (S)

(R)-BINAP (**4.6**): 75% conv (16h), 34% ee (S)
(R)-(S)-Josiphos (**4.12**): 62%conv (16h), 36% ee (S)

Figure 4.7: Substrate scope for the phosphine-mediated asymmetric β-boration reaction. Conditions: Substrate (0.5 mmol), chiral auxiliary (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 mmol), THF, 70ºC, 6h

Considering the mechanism it should be mentioned that Hoveyda and coworkers[11] postulated that carbene interacted with the diboron reagent and activated it. Since in our system there are two nucleophiles, Lewis bases (phosphine and methoxyde), and two electrophiles (the diboron reagent and the substrate), it is more complex than Hoveyda's system. While the interaction of the MeO^- and the diboron reagent has been clarified both experimentally and theoretically, as discussed previously in this chapter, up to now we have not found any clear spectroscopical evidence of an interaction between the phosphine and the diboron reagent. However, the high levels of enantioselectivity could indicate that the chiral auxiliary must be close enough to the active site when the C-B bond formation takes place in order to transmit the enantiodifferentiation. We have postulated the possibility that the phosphine interacts with the substrate forming a phosphonium type intermediate. It could be followed by a nucleophilic substitution (probably SN_2 fashion), where the nucleophilic boryl moiety replaces the phosphine moiety (Scheme 4.8). Note that, according with the preliminary calculation carried out by Ms C. Pubill-Ulldemolins and Dr. C. Bo, C_β-P bond does not need to be fully formed before the nucleophilic attack by the activated diboron reagent. This postulated mechanism could operate simultaneously with the previously suggested for the organocatalytic β-boration, based on only methanol and base, and also could explain why when less amount of base was used better enenatioselectivities were obtained (Table 4.6, entries 1 and 3). The enantioselectivity of the product might be directly related to a series of aspects: a) How much is the formation of this phosphonium intermediate favored? b) How does the steric hindrance of the phosphonium intermediate affect the discrimination? c) How much is the nucleophilic substitution of this phosphonium intermediate favored compared to the nucleophilic attack at the substrate? The suggested mechanism is currently being investigated by experimental and theoretical methods.



Scheme 4.8: Hypothetical competitive catalytic cycles in base/alcohol catalyzed organocatalytic β-boration reaction and phosphine assisted organocatalytic β-boration reaction

4.4 Analysis of the results and limitations

We have developed a new methodology for organocatalytic β-boration reaction using methanol and base as catalytic system to activate the diboron reagent, generating a polarized diboron adduct. The sp^2 boryl moiety of the adduct has gained enough electron density to perform the nucleophilic attack at the β position of the α,β-unsatutared carbonyl compounds.

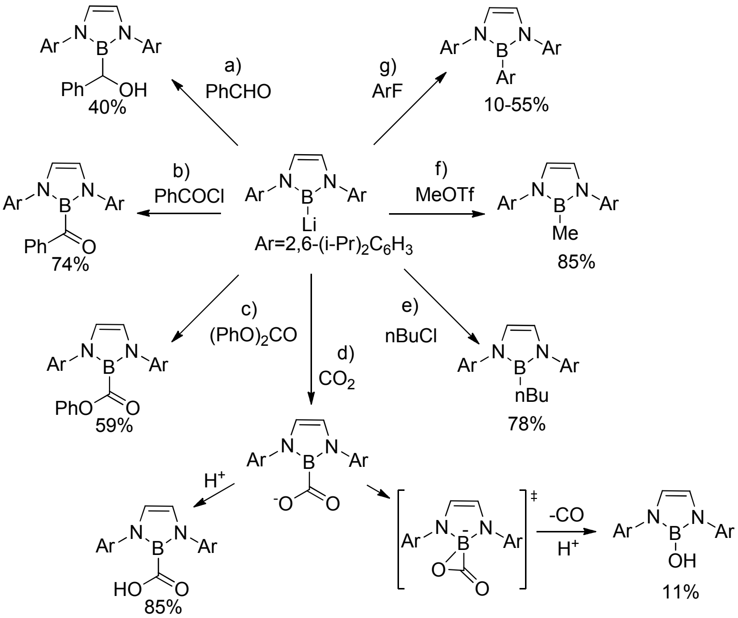
A notable difference between Hoveyda's methodology and ours is that with our methodology we do not need a N-heterocyclic carbene to activate the diboron. The sole use of alkoxy anion is enough to promote the reaction. Another important difference is the assistance of phosphine, both in the activity and enantioselectivity of the interaction between the $[MeO\rightarrow Bpin\text{-}Bpin]^-$ and the substrate. To the best of our knowledge, asymmetric induction with Hoveyda's method has not been achieved or reported.

The organocatalytic system is less active than the metal-mediated β-boration reaction. α-Substituted substrates or β-aryl substrates are not readily converted into the desired product. Also elevated temperatures (70ºC) are required to obtain synthetically useful conversions in comparison with the metal mediated systems.

4.5 Current overview of metal free nucleophilic boron addition after our contribution

In the course of the last years, the metal free nucleophilic boron addition to unsaturated molecules has become an important topic, which is rapidly progressing.

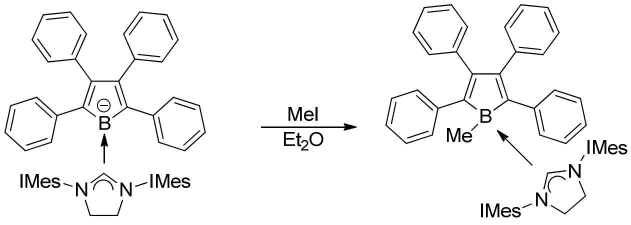
The first isolated diamino-substituted boryllithium compound was shown to react with a variety of organic electrophiles (Scheme 4.9).[13] In general, the reactivity with carbonyl groups gave the corresponding products in the same way as carbanions react. For instance, the boryl moiety attacked the carbonyl group of benzaldehyde to afford, upon subsequent protonation, the corresponding α-borylbenzyl alcohol (Scheme 4.9a). The reaction of the diamino-substituted boryllithium with benzoyl chloride gave the substituted benzoylborane product (Scheme 4.9b), while the reaction with anhydrous carbonates afforded the corresponding borylcarboxylate ester product (Scheme 4.9c). The reaction with carbon dioxide followed by protonation provided a borylcarboxylic acid in high yields with a small amount of hydroxyborane as by-product (Scheme 4.9d). A plausible mechanism of the formation of the hydroxyborane was suggested on the basis of an intramolecular cyclization, followed by CO elimination from the borylcarboxylate anion to afford the corresponding boronate, which was protonated to give the hydroxyborane. The reaction of the diamino-substituted boryllithium with 1-chlorobutane in THF gave *n*-butylborane (Scheme 4.9e), while its reaction with methyl trifluoromethanesulfonate provided methylborane (Scheme 4.9f). Remarkably, the reaction of this diamino-substituted boryllithium with ArF (Ar=Ph) yielded phenylborane, although in a low yield because the reaction is slower than the decomposition of the boryllithium (reaction time 12h). The reactivity could be improved when Ar= C_6F_5 in ArF reagent, affording the pentafluorophenylborane in a moderate yield within shorter reaction times (Scheme 4.9g). These experiments demonstrated that the boryllithium compounds behaved as nucleophiles, and reacted with organic electrophiles via a wide range of mechanisms such as nucleophilic substitution, nucleophilic addition, nucleophilic addition/elimination and nucleophilic aromatic substitution.[13]



Scheme 4.9: Reactivity of the diamino-substituted boryllithium compound with various organic electrophiles

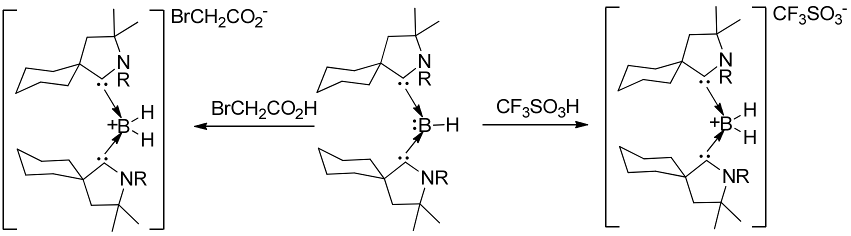
The nucleophilic character of the boryl anion allows its use as a ligand. In the last years, several complexes have been synthesized from the most common coinage metals (Au, Ag and Cu)[14], Mg, Zn, Ti[15] and rare-earth metals.[16]

In 2010, N-heterocyclic carbenes stabilized borole compounds showing π nucleophilic boron character, which clearly reacted with electrophiles such as MeI. This reaction represents the first example of reactivity employing this kind of boron heterocycle (Scheme 4.10).[17]



Scheme 4.10: Reactivity of NHC stabilize a borole compound

Recently, Bertrand and coworkers have developed the latest example of nucleophilic boron reagent isolating a bis(carbene)BH adduct.[18] The boron in this compound is in the formal oxidation state +1 and is clearly electron-rich. The presence of a lone pair of electrons at the boron of the bis(carbene)BH adduct renders it nucleophilic and it can be expected to have the potential to react with electrophiles. Indeed, it has been reported that the bis(carbene)BH adduct reacted with an equimolar amount of trifluoromethane sulphonic acid at room temperature, and after the work up the conjugate acid was isolated in 89% yield (Scheme 4.11). The solid state structure confirmed the formation of a tetracoordinate boron compound, with two hydrogen atoms directly bonded to boron generating a boronium cation. Similar reactivity has been observed with $BrCH_2CO_2H$ (Scheme 4.11).



Scheme 4.11: Reactivity of bis(carbene)BH adduct

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Luck is what happens when preparation meets opportunity.

Seneca

5 Organocatalytic diboration and its enantioselective approach

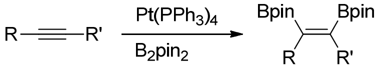
Table of contents

5.1 Introduction

The chemistry of boron is rich, exciting, and extremely important in organic synthesis due to the versatile transformations of the C-B bonds.[1] For this reason any attempt to develop new efficient strategies to add boryl units to organic molecules have a tremendous interest. In this context, diboration is one of the most efficient reactions in organic synthesis, because it introduces simultaneously two boryl units in the unsaturated molecule with total atom economy. When both C-B bonds are formed, they can be functionalized independently to produce homodifunctionalized or heterodifunctionalized compounds.

The activation of the diboron reagent has always been associated with the use of transition metal complexes, but why are metal catalysts required for the diboration of unsaturated substrates? It is known, for example, that the diboron tetrahalide B_2Cl_4 could be added to double and triple bonds in the absence of catalyst.[2] However the diboron tetrahalides are rather difficult to prepare and handle and are unstable to disproportionation. In contrast, the tetraalkoxidiboron compounds, such as the structurally characterized B_2cat_2 and B_2pin_2,[3] are easy to prepare *via* $B_2(NMe_2)_4$ and are quite stable, however they cannot be added to alkenes or alkynes under conventional reaction conditions.[4] Thus, the use of transition metal catalysts is required to cleave the B-B bond of the tetraalkoxidiboron reagent.

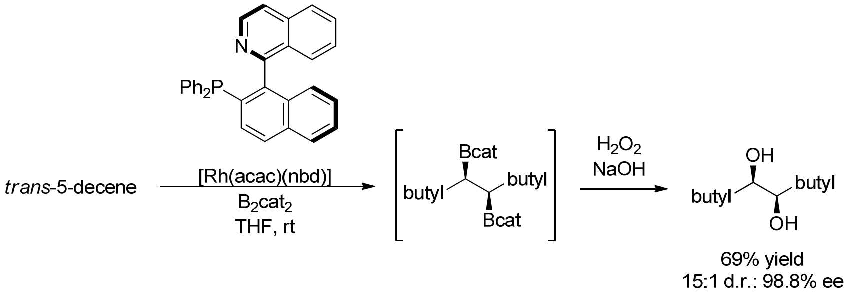
The first transition metals used in the catalytic diboration reaction of alkynes and alkenes were Pt and Rh (Scheme 5.1).[5] In these cases the diboron reagent was oxidatively added to the metal center generating the diboryl units coordinated to the metal.



Scheme 5.1: First diboration reaction using tetraalkoxidiboranes

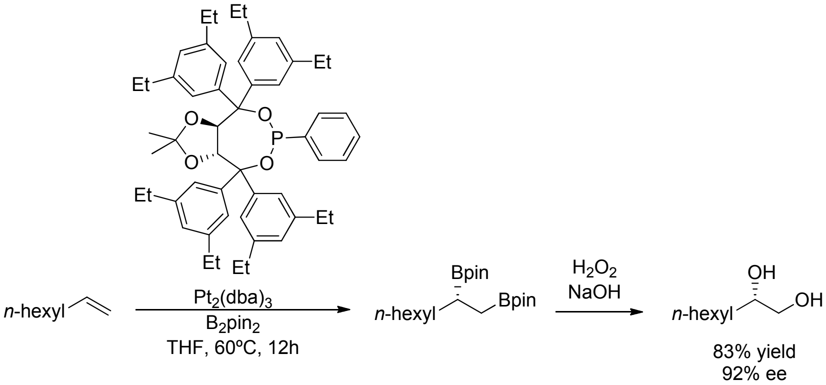
Depending on the nature of the metal center and the alkene substrate, the diboration reaction could not be selective due to the β-hydride elimination side reaction.[5b] In order to avoid the formation of byproducts, different strategies have been designed, but the use of transition metals in which the formation of M-H bond is disfavored, usually transition metals with lower *d* orbital energies, has been very well accepted in the last decade. In general, these transition metals fail to activate the diboron *via* oxidative addition and normally interact with the tetraalkoxidiboranes without changing their oxidation state, *via* σ-bond metathesis. This methodology provides excellent levels of chemoselectivity towards the diborated product. Our group also has contributed to this area using coinage metals modified with N-heterocyclic carbenes and phosphines.[6]

The use of transition metals to activate the diboron reagents provides the opportunity to select chiral ligands that modify the metal center in order to transfer the enantioselectivity to the diborated product.[7] The first generation of enantioselective catalysts included rhodium complexes modified with (R)-QUINAP as ligand (Scheme 5.2),[8] which provided high enantioselectivities in the diboration of simple alkenes although the selectivity was not always complete towards to the diborated product.



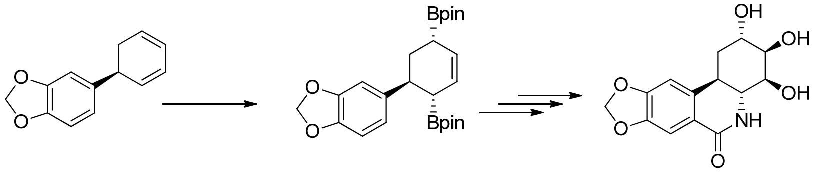
Scheme 5.2: Rh / (R)-Quinap catalytic system mediated enantioselective diboration of alkenes

In the following years, the substrate scope increased with the Pd-mediated enantioselective diboration of allenes and Pt-mediated the enantioselective diboration of dienes using phosphite and phosphoramidites as chiral ligands.[9] Recently, Morken and coworkers have developed an enantioselective diboration methodology for terminal alkenes using Pt(0) precursors and phosphonites as ligands, obtaining enantioselectivities up to 92% (Scheme 5.3).[10]



Scheme 5.3: Pt / phosphonites system mediated enantioselective diboration of alkenes

The interest of the enantioselective boron addition in organic synthesis is related to the possibility to transform simple alkenes into molecules with high value. As an example, the enantioselective diboration of dienes which generates two new enantioselective C-B bonds, which was the key step in the synthesis of (+)-*trans*-dihydrolycoricidine (Scheme 5.4), a natural product.[11]



Scheme 5.4: Enantioselective diboration applied to the total synthesis of (+)-*trans*-dihydrolycoricidine

5.2 Work hypothesis

Continuing with the application of the nucleophilic boryl attack from [MeO→Bpin-Bpin]$^-$ adduct to unsaturated molecules, we focused an less activated C=C double bonds as substrates. We became also interested in finding the method that optimizes the use of diboranes from an atom economical perspective. Taking into consideration the polarization of B-B bond in the [MeO→Bpin-Bpin]$^-$ adduct, and the fact that one of the boryl unit has a nucleophilic character and the other has a electrophilic behavior, could it be possible to interact both boryl units with simple alkenes?

The use of alcohols to generate in situ the Lewis acid-base adducts implies the opportunity of the application of chiral alcohols in order to transfer chirality to the final product. How efficient could the chiral transmition be from the chiral alkoxi group to the prochiral substrate?

5.3 Results and discussion

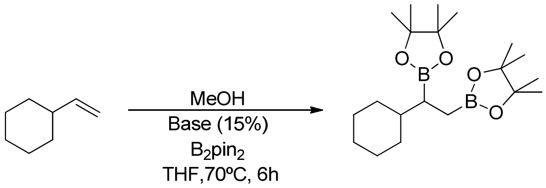
Hitherto, we had worked in the organocatalytic β-boration of α,β-unsaturated carbonyl compounds. In these unsaturated molecules, the carbonyl functionality acts as an electronwithdrawing group, transforming the simple alkenes in activated olefins. Next, we selected styrene as an alternative to the activated olefins, considering that the conjugation of the double bond with the aryl group might provide a slight activation.

When we added the B_2pin_2 reagent to the substrate, in the presence of MeOH/base, styrene was transformed into a mixture of the expected hydroborated product and, surprisingly, the diborated product as well. The formation of the later product was completely unexpected. In order to get more information, we tested the same reaction changing the substrate to the non activated analogous, vinyl cyclohexane. To our surprise, and satisfaction, only the diborated product was observed by ^1H NMR.

This is the first case, in which both boryl moieties of the tetraalkoxidiborane reagent could be added to an olefin without the mediation of transition metal catalysts. Being aware of the interest in this discovery, we intended to optimize the reaction conditions.

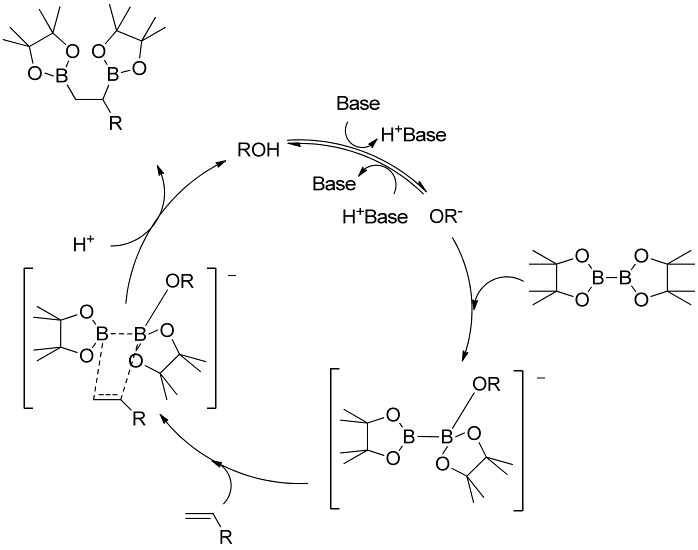
First of all, we screened the bases, which have a crucial role in the generation of the alkoxide that interacts with B_2pin_2. Cesium carbonate was used as base in our first experiment and provided excellent conversion and chemoselectivity towards the diborated product (Table 5.1, entry 1). Comparable conversions were obtained with other metal carbonates or alkoxides (Table 5.1, entries 2, 4-7). No differences were observed using different metal alkoxides such as sodium *tert*-butoxide or sodium methoxide bases (Table 5.1, entries 4 and 5). We also realized that the cation of the metal methoxide base (M = Na, Li and K) did not influence the reaction outcome (Table 5.1, entries 5-7). The use of weaker bases strongly affected the conversion, for example the change of potassium carbonate to potassium hydrogencarbonate diminished the conversion to 45% (Table 5.1, entries 2 and 3). The use of methanol was also crucial, because in its absence KOMe could only promote the reaction stoichometrically (Table 5.1, entry 8). This suggested that the role of MeOH might also be involved in the regeneration of the active species. (Scheme 5.5).

Table 5.1: Influence of bases and methanol in the organocatalytic diboration



Entry	Base	Alcohol	Conv (%)	Chemo (%)
1	Cs_2CO_3	MeOH	94	92
2	K_2CO_3	MeOH	86	91
3	$KHCO_3$	MeOH	45	96
4	NaO*t*Bu	MeOH	89	96
5	NaOMe	MeOH	91	98
6	LiOMe	MeOH	86	99
7	KOMe	MeOH	90	97
8	KOMe	-	16	65
9	Cs_2CO_3	-	7	-

Standard conditions: vinyl cyclohexane (0.5 mmol), bis(pinacolato)diboron (0.55 mmol), base: (15 mol %), MeOH (100 μl, 5eq.), solvent: THF (2mL). 70ºC, 6h. Conversion and chemoselectivitiy determined by GC and ^{1}H NMR.

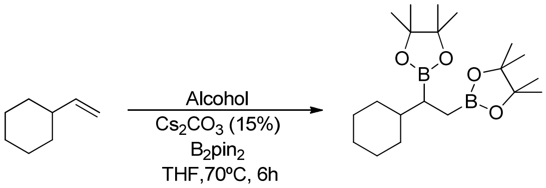


Scheme 5.5: Hypohtetical catalytic cycle of organocatalytic diboration.

The hypothetical catalytic cycle starts with the formation of the alkoxide from base and methanol. The alkoxide could interact with the diboron reagent generating the Lewis acid-base adduct, like in the mechanism of the organocatalytic β-boration reaction (C*hapter 4*). The hardest part to postulate, in this hypothetical catalytic cycle, is the interaction between the adduct and the C=C double bond. This interaction could be explained by a concerted nucleophilic/electrophilic attack of the [RO→Bpin-Bpin]$^-$ to the double bond. As a consequence of this interaction the formation of both C-B bonds would be guaranteed. This postulated catalytic cycle might explain the slow reaction rate in the absence of methanol.

It has been observed that the presence of methanol is required to convert the organocatalytic diboration from a stoichiometric approach to a catalytic approach. For that reason, after the screening of bases, we carried out a systematic study using different alcohols in the organocatalytic diboration reaction, in order to know more about the influence of the alcohol structure in the reaction. We could observe a trend between the activity and selectivity of the diboration of vinylcyclohexane and the Lewis basicity of the corresponding alkoxide. The increased Lewis basicity facilitates the formation of the adduct, as a direct dependence of electronic effects (MeO$^-$, EtO$^-$, BuO$^-$ > $CF_3CF_2O^-$, PhO$^-$) and steric effects (MeO$^-$ > EtO$^-$ > *i*PrO$^-$ > *t*BuO$^-$) (Table 5.2).

Table 5.2: Influence of the nature of the alcohol in the organocatalytic diboration



Entry	Alcohol	Conversion (%)	Chemoselectivity (%)
1	MeOH	94	92
2	EtOH	90	89
3	CF_3CF_2OH	81	96
4	BuOH	86	87
5	*i*PrOH	61	74
6	PhOH	40	95
7	*t*BuOH	35	62

Standard conditions: vinyl cyclohexane (0.5 mmol) bis(pinacolato)diboron (0.55 mmol) Cs_2CO_3: (15 mol %), alcohol (5 eq.), solvent: THF (2mL). 70ºC, 6h, Conversion and chemoselectivitiy determined by GC and ^{1}H NMR.

Once we established that methanol was the best alcohol for the diboration reaction, we studied which was the optimum quantity of this alcohol. Consequently, a series of experiments varying the amount of alcohol (0-10 eq.) were carried out under the standard reaction conditions. Low conversion was achieved when small amount of methanol were used, moreover when we increased the amount of methanol the conversion of the substrate increased logarithmically (Figure 5.1). The chemoselectivity towards the diborated product (versus the hydroborated product) varied between 80-90%. The chemoselectivity vs. amount of methanol function had a maximum at 5 eq. of MeOH.

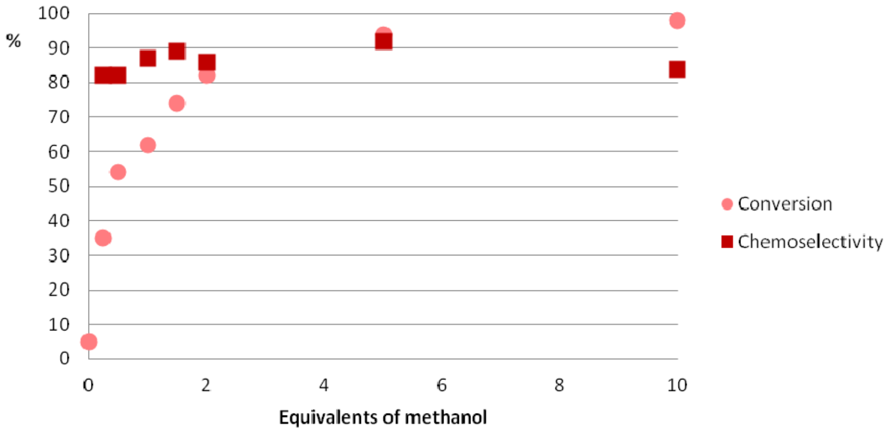
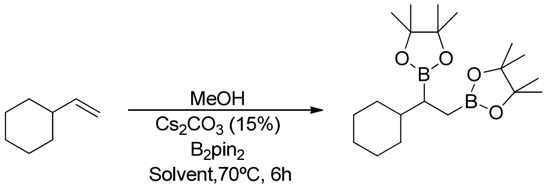


Figure 5.1: Influence of equivalents of methanol in the conversion and chemoselectivity of organocatalytic diboration of vinylcyclohexane.

Another interesting finding in this study was the influence of the nature of the solvent in the organocatalytic diboration. The reaction was tested in polar solvents (THF and DMF) and apolar solvents (toluene and cyclohexene). Polar solvents provided better conversions than apolar solvents (Table 5.3, entries 1-2 and 3-4), probably due to better solvation of the polar components of the system. As far as the temperature of the reaction is concerned, the higher temperature provided better conversion and similar chemoselectivity. (Table 5.3, entry 1 and 5).

Table 5.3: Influence of the solvent in the organocatalytic diboration



Entry	Temperature (ºC)	Solvent	Conversion (%)	Chemoselectivity (%)
1	70	THF	94	92
2	70	DMF	89	95
3	70	Toluene	2	-
4	70	Cyclohexane	51	91
5	45	THF	89	95

Standard conditions: vinyl cyclohexane (0.5 mmol) bis(pinacolato)diboron (0.55 mmol), Cs_2CO_3: (15 mol %), MeOH (100 μl 5 eq.), solvent: THF (2mL). 70ºC, 6h, Conversion and chemoselectivitiy determined by GC and ^{1}H NMR.

The simple organocatalytic system was capable to mediate the addition of the most common and commercial available diboron reagents to non-activated olefins. We found that bis(pinacolato)diboron is the most reactive and selective diboron reagent towards the diborated product, although other tetraalkoxidiboranes such as bis(catecholato)diboron, bis(hexylideneglycolato)diboron and bis(neopentylglycolato)diboron also provided moderate to high yields (Figure 5.2).

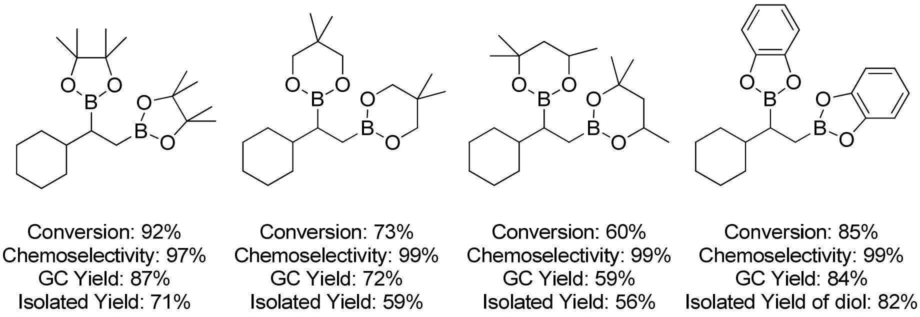
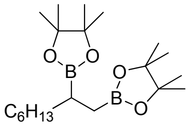
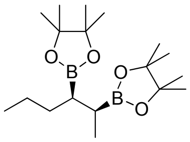


Figure 5.2: Influence of the most common and commercially available diboron reagents on the organocatalytic diboration reaction

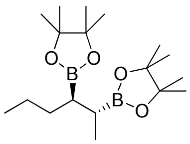
Keeping bis(pinacolato)diboron as the diboron reagent of choice, we wanted to extend the substrate scope of the reaction. Terminal olefins such as 1-octene could be selectively transformed into the diborated product within 6h at 70ºC (Figure 5.3). The diboration of the styrene required lower temperatures (45ºC) in order to obtain high chemoselectivity. Internal alkenes gave some indirect information about the mechanism of the reaction, as in our case the organocatalytic diboration always occurred in syn fashion. *Trans*-2-hexene gave the diborated product in 3:97 syn/anti ratio and *cis*-2-hexene gave the diborated product in a 95:5 syn/anti ratio (Figure 5.3). Similarly, 2-cyclohexene provided exclusively the syn product. We could observe that the cis olefin reacted faster than the trans olefin providing higher yields of the diborated product (Figure 5.3). Another finding is that the organocatalytic diboration of allenes favored the formation of the 1,2-diborated product in contrast to the transition metal catalyzed diboration, which usually provides the 2,3-diboration product.[7]



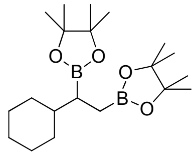
15% Cs_2CO_3, 70ºC, 6h
Conversion: 98%
Chemoselectivity: 99%
GC Yield: 97%
Isolated Yield: 71%



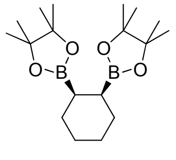
15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 95%
Syn/Anti: 95:5
GC Yield: 83%
Isolated Yield: 69%



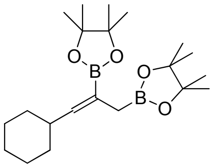
15% Cs_2CO_3, 70ºC, 6h
Conversion: 74%
Chemoselectivity: 96%
Syn/Anti: 3:97
GC Yield: 69%
Isolated Yield: 57%



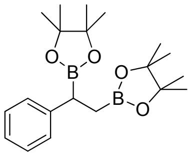
15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 97%
GC Yield: 87%
Isolated Yield: 71%



15% NaO*t*Bu, 70ºC, 16h
Conversion: 84%
Chemoselectivity: 99%
GC Yield: 83%
Isolated Yield: 65%



15% NaO*t*Bu, 45ºC, 20h
Conversion: 95%
Chemoselectivity: 92%
Selectivity 1,2-Diboration: 87%
GC Yield: 76%



15% NaO*t*Bu, 45ºC, 15h
Conversion: 82%
Chemoselectivity: 99%
GC Yield: 81%
Isolated Yield: 74%

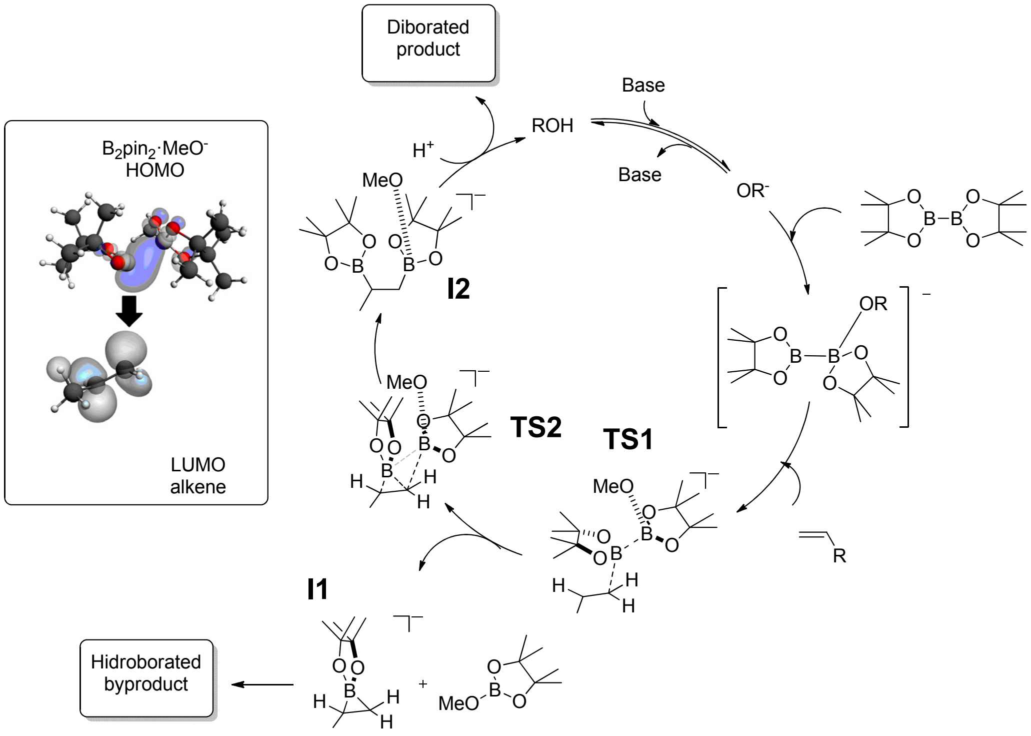
Figure 5.3: Substrate scope of the organocatalytic diboration

To establish the mechanism of the reaction, we envisioned a catalytic cycle in which methoxide anion, generated in situ from methanol and base, activated the diboron reagent. Similar adduct formed from B_2pin_2 and

KO*t*Bu was reported by Marder and coworkers.[12] To find evidences for the subsequent steps of the catalytic cycle, we started a collaboration project with Dr. C. Bo and Ms C. Pubill-Ulldemolins (in the framework o a cosupervised thesis with Dr. Elena Fernández) to study the possible interactions between a model substrate (propylene) and the adduct, using various DFT methods.[13]

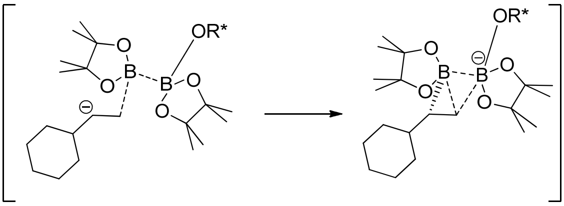
In the organocatalytic β-boration reaction we postulated and demonstrated the formation of the $[\text{MeO}\rightarrow\text{Bpin-Bpin}]^-$ Lewis acid-base adduct by both experimental and theoretical methods. The interaction of the methoxide with the B_2pin_2 polarized the B-B bond, providing the sp^2 boryl unit with a nucleophilic character.

Ms C. Pubill-Ulldemolins and Dr. C. Bo identified theoretically two transition state structures (TS1, TS2) and two intermediates (I1, I2) according to the possible interactions between the $[\text{MeO}\rightarrow\text{Bpin-Bpin}]^-$adduct and the model substrate, propylene (Scheme 5.6). TS1 derives from the interaction of the activated diboron and the less hindered carbon of the C=C double bond. According to the theoretical calculations, this interaction is an overlap of the strongly polarized B-B σ-orbital (HOMO) and the antibonding π* orbital (LUMO) of the olefin. Thus, the interaction can be described as a nucleophilic attack from the activated diboron towards the non-activated olefin, representing an almost unknown reactivity for this type of substrates. Upon the nucleophilic attack, while the Bsp^2-C_1 bond was being formed, the B-B bond is becoming weaker, and the electrondensity was increasing on C_2. Nucleophilic attack from C_2 towards the Bpin moiety could lead to the formation of I1 and TS2. If the electronic and steric effects stabilize the C_1-Bsp^2 interaction, the I1 is formed towards the hydroborated byproduct. On the other hand, if C_1 attacks at the Bpin(OMe) moiety, the TS2 could be formed towards the formation of the diborated product. (Scheme 5.6).



Scheme 5.6: Adaptation of the postulated theoretical mechanistic cycle of organocatalytic diboration reactions of alkenes

Having identified the appropriate conditions and taking into consideration the plausible mechanism of the reaction, we were really interested in inducing asymmetry in the organocatalytic diboration of non-activated olefins. From the results obtained with the theoretical calculations we knew more about the role of the $[MeO\rightarrow Bpin\text{-}Bpin]^-$ adduct, and we concluded that the use of chiral alcohols could be a possible approach to obtain asymmetric induction in the organocatalytic diboration reaction (Scheme 5.7).



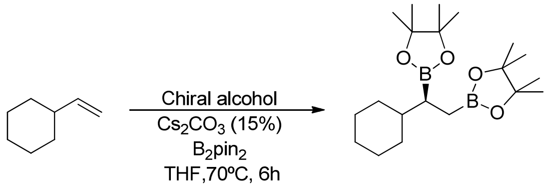
TS1 **TS2**

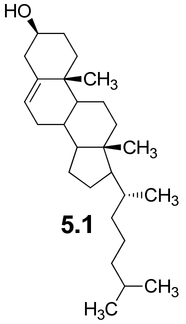
Scheme 5.7: Hypotetical asymmetric approach on the organocatalytic diboration.

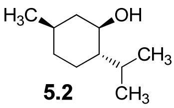
We choose chiral alcohols as chiral auxiliaries for the diboration reaction because chiral alcohols are often cheap and readily available in the nature. We were aware that the use of secondary or tertiary chiral alcohols could diminish the activity of the organocatalytic system because the formation of the [RO→Bpin-Bpin]$^-$ adduct with substituted alcohols is less favored. Therefore, we focused our initial efforts on primary and secondary chiral alcohols reducing the amount from 5 eq. to 2 eq. for economical reasons, assuming the possibility to obtain lower conversions and selectivities towards to the diborated product.

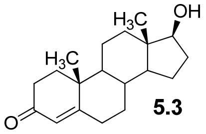
To initiate the asymmetric organocatalytic diboration reaction, a small but representative library of alcohols was selected (**5.1-5.10**) (Table 5.4). Primary alcohol **5.5**, derivative from pyranose carbohydrate, was rather efficient in transforming the vinylcyclohexane into the diborated product, but the enantioselectivities, in general, were low (Table 5.4). Only (S)-1-Phenylethanol (**5.10**) induced enantioselectivity up to 24%, although the conversion was low and the chemoselectivity was only moderate (Table 5.4, entry 10).

Table 5.4: General screnning of chiral alcohols for asymmetric organocatalytic diboration




5.1


5.2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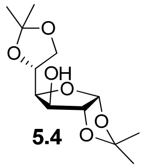
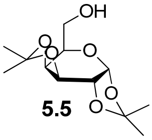
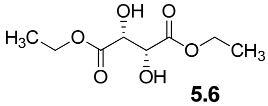
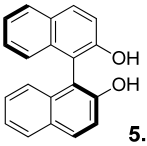
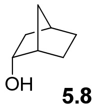
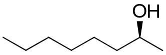

5.4

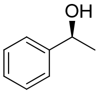

5.5


5.6


5.7


5.8


5.9

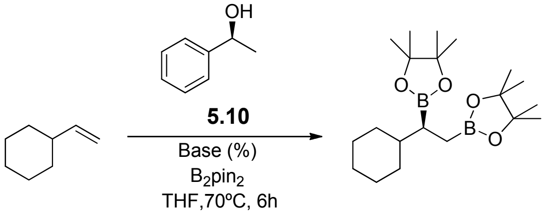

5.10

Entry	Alcohol	Conversion (%)	Chemoselectivity (%)	Ee (%)
1	**5.1**	<5	-	-
2	**5.2**	47	73	13 (S)
3	**5.3**	<5	-	-
4	**5.4**	9	95	1 (S)
5	**5.5**	85	87	10 (R)
6	**5.6**	<5	-	-
7	**5.7**	<5	-	-
8	**5.8**	34	67	9
9	**5.9**	36	63	9
10	**5.10**	33	65	24 (S)

Conditions: Cs_2CO_3 (15% mol), alcohol (2 eq), Bis(pinacolato)diboron (1.1 eq), substrate (0,25 mmols), (1mL), THF, 70ºC, 6h. Conversion and chemoselectivitiy determined by GC and ^1H NMR. Enantioselectivity from the acylated product determined by GC-MS.

These initial results encouraged us to improve the yield of the diborated product. We did a general screening of the reaction conditions, keeping constant the amount of chiral alcohol for economical reasons (Table 5.5).

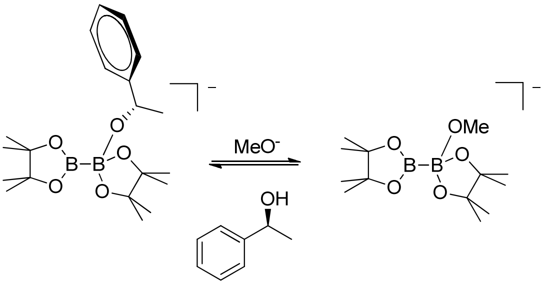
Table 5.5: Optimization of the reaction conditions in the asymmetric organocatalytic diboration



Entry	Base (%)	Solvent	Time (h)	Temp (ºC)	Conv (%)	Chemo (%)	Ee (%)
1	Cs_2CO_3 (15%)	THF	6	70	33	65	24 (S)
2	Cs_2CO_3 (15%)	THF	16	70	66	61	21 (S)
3	Cs_2CO_3 (15%)	THF	16	45	49	86	23 (S)
4	Cs_2CO_3 (80%)	THF	16	45	78	85	22 (S)
5	Cs_2CO_3 (100%)	THF	16	45	91	83	24 (S)
6	Cs_2CO_3 (120%)	THF	16	45	85	82	21 (S)
7	Cs_2CO_3 (200%)	THF	16	45	80	75	22 (S)
8	K_3PO_4 (100%)	THF	16	45	29	80	20 (S)
9	NaOtBu (100%)	THF	16	45	87	96	17 (S)
10	NaOMe (100%)	THF	16	45	88	96	10 (S)
11	Cs_2CO_3 (100%)	Toluene	16	45	83	89	27 (S)
12	Cs_2CO_3 (100%)	DCM	16	45	96	91	24 (S)
13	Cs_2CO_3 (100%)	DCM	16	25	40	85	21 (S)

Conditions: Base (% mol), alcohol **5.10** (2 eq), Bis(pinacolato)diboron (1.1 eq), substrate (0.25 mmols), solvent (1mL). Conversion and chemoselectivitiy determined by GC and ^{1}H NMR. Enantioselectivity from the acylated product determined by GC-Ms.

Our first experiments indicated that 16h of reaction time was required for synthetically useful conversions (Table 5.5, entries 1-2). Temperature had a dramatic effect on the activity and chemoselectivity of the reaction. Lower temperature provided better selectivities towards the diborated product, unfortunately without any significant increase of the enantioselectivity (Table 5.5, entries 2-3). Increasing the amount of base resulted in a steady increase of the conversion up to 91%, at 1 equivalent of base (with respect to the substrate) (Table 5.5, entries 3-7). Phosphate provided low conversions (Table 5.5, entry 8) and, metal alkoxides such us NaOMe or NaO*t*Bu (Table 5.5, entries 9-10) decreased the enantioselectivity. This could be due to competitive formation of [MeO→Bpin-Bpin]$^-$ or [*t*BuO→Bpin-Bpin]$^-$ which produces the racemic diborated product. (Scheme 5.8).



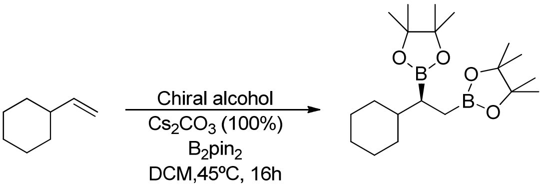
Scheme 5.8: Equilibrium between chiral and achiral adduct when alkoxide base was used

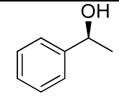
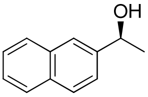
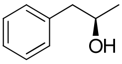
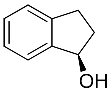
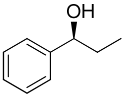
Other diboron reagents such as bis(cathecolato)diboron, bis(neopentylglycolato)diboron and bis(hexylideneglycolato)diboron have been tested in the reaction displaying poor activities with similar selectivities and enantioselectivities towards to the diborated product.

We carried out the model reaction using other structurally related secondary alcohols with some steric and electronic differences to tune the chiral auxiliary.

α-Substituted benzyl alcohols (**5.11**, **5.12**, **5.14**, **5.15**) provided better activities and enantioselectivities than 2-phenylethanol derivates **5.13** (Table 5.6, entry 3). Increasing the steric bulk of the alkyl substituent of the benzyl alcohol, such as the change of the methyl for ethyl, provided also a slight increase of the stereoselectivity achieving enantioselectivities up to 39% (Table 5.6, entry 5).

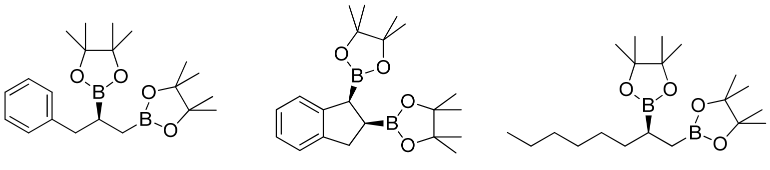
Table 5.6: Screening of chiral alcohols for asymmetric organocatalytic diboration reaction



Entry	Alcohol	Conversion (%)	Chemoselectivity (%)	Ee (%)
1	 **5.11**	96	91	24 (S)
2	 **5.12**	83	84	18
3	 **5.13**	50	70	3
4	 **5.14**	90	86	33
5	 **5.15**	70	87	39

Conditions: Cs_2CO_3 (100% mol), alcohol (2 eq.), bis(pinacolato)diboron (1.1 eq.), substrate (0.25 mmols), DCM (1ml), 45ºC, 6h. Conversion and chemoselectivitiy determined by GC and ^{1}H NMR. Enantioselectivity from the acylated product determined by GC-MS.

To extend this approach to similar substrates, the chiral auxiliary **5.15** was selected. The enantioselectivity found for allylbenzene was the highest, 42% (Figure 5.4).



42% ee 26% ee 31% ee

Figure 5.4: Small substrate scope for asymmetric organocatalytic diboration.

5.4 Analysis of the results and limitations

Organocatalytic diboration represents a great advance in the simultaneous formation of two C-B bonds simultaneously. For the first time, this reaction could be carried out without transition metals, using tetraalkoxidiboranes as reagent, under mild reaction conditions and in short reaction times. It represents a good example of atom economy but also of simplification of synthetic routes.

The methodology is useful for simple, terminal and internal, alkenes. However, preliminary studies on the organocatalytic diboration of alkynes have shown lower chemoselectivities with mixtures of hydroborated, diborated and polyborated products. Also, substituted olefins or electro-deficient olefins such as stilbene displayed with low reactivities and poor chemoselectivities.

We have been able to induce asymmetry by using 2 eq. of accessible chiral alcohols, but the enantioselectivities have not exceeded 41%. This is a current limitation, however still there are many other chiral alcohols to be explored and alternative methodologies in order to optimize the asymmetric version with a real balance between efficiency and economy.

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> *The trail is the thing, not the end of the trail. Travel too fast, and you miss all you are traveling for.*
>
> ***Louis L'Amour***

6 Conclusions

6.1 ***Chapter 2:*** *(NHC)Copper mediated β-boration of activated olefins*

Our current understanding of the (NHC)Cu(I) mediated β-boration of α,β-unsaturated carbonyl substrates suggests that in the absence of base the precursor of catalyst (NHC)CuOR could react with bis(pinacolato)diboron to form the corresponding (NHC)Cu-boryl intermediate easier than (NHC)CuCl. In our study, the base seems to be crucial in favouring the heterolytic cleavage of the diboron, promoting the σ-bond metathesis and stabilizing the second boryl unit as a ROBpin.

The use of NHC-s as ligands in Cu mediated β-boration of α,β-unsaturated aldehydes guaranteed high conversion of the substrate into the desired β-borated aldehyde, diminishing the secondary 1,2-diboron addition.

The challenge of enantiofacial differentiation in the conjugate borylation of α,β-unsaturated carbonyl compounds was overcome using copper salts modified with chiral NHC ligands, although enantiomeric excess values were moderate. Even so, our contribution certainly expanded the portfolio of the stereocontrolled conjugated borylation.

In this work we have demonstrated that NHC chiral ligands could be an alternative to the traditional diphosphine ligands, and concluded that the C_1 symmetry in the NHC ligand provided higher enantioselectivities in (NHC)Cu(I) mediated β-boration reaction.

6.2 ***Chapter 3:*** *Palladium and Iron mediated β-boration reaction*

Palladium complexes have been applied satisfactorily in the β-boration reaction of a large scope of α,β-unsaturated esters, ketones, aldehydes and amides. We have found interesting that the same palladium complex precursor mediated the two consecutive reactions: β-boration of α,β unsaturated carbonyl compounds and cross coupling of the organoboronates with arylbromides. The two consecutive catalytic reactions were performed in a one pot system. However, this methodology could not be extended to the cross-coupling of internal β-boryl carbonyl compounds.

Iron salts facilitated the β-boration reaction but, under the same reaction conditions, the iron system seemed to be less active than the palladium, copper or nickel systems. However, the advantages of iron in terms of economical and environmental factors could counteract their deficiencies in terms of activity.

Despite the encouraging asymmetric approach (ee up to 69% with Fe / phosphoroamidite ligand) obtained in the iron assisted β-boration reaction, there is a remaining important question to be answered. How is the diboron reagent activated in this reaction and how interact the pinacolboryl unit with the α,β-unsaturated esters in an enantiodifferentiating fashion?

6.3 ***Chapter 4:*** *Organocatalytic β-boration of α,β-unsaturated carbonyl compounds*

We have developed a new methodology, the organocatalytic β-boration reaction. Alkoxide ion was generated in situ from the base and the alcohol. The corresponding alkoxide interacts with the diboron reagent generating the activated adduct [MeO→Bpin-Bpin]$^-$ and could be added to a large scope of α,β-unsaturated carbonyl compounds.

In contrast with Hoveyda's methodology, our system does not need a carbene to activate the diboron reagent, the alkoxyde is enough to promote the reaction. On the other hand, our methodology requires higher temperatures to obtain good yields. Another difference is that when we add catalytic amounts of phosphine, as a chiral auxiliary component, high levels of esteroselectivity (ee up to 95%) could be achieved. This is another important difference with Hoveyda's methodology in which enantioselectivity has not yet been reported.

This organocatalytic system is less active than the metal-mediated β-boration reaction and sterically hindered substrates became more difficult to β-borate. From the enantioselective point of view, while copper modified with Josiphos ligand allowed high conversions and enantioselectivities for a broad scope of substrates, our methodology needed a special chiral auxiliary for each small group of substrates.

6.4 **Chapter 5:** *Organocatalytic diboration and its enantioselective approach*

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

The methodology is useful for a broad scope of alkenes, but more studies are required to optimize the system for other non-activated unsaturated substrates. Preliminary studies show that the reaction with alkynes proceeds with low selectivities, leading to mixtures of hydroborated, diborated and polyborated products. Also, substituted olefins or electron-deficient olefins, such as stilbene, display low reactivities and poor chemoselectivities.

An enantioselective approach has been developed, for the first time, in a metal-free version, selecting chiral alcohols as the chiral auxiliary component of the reaction. Currently, the optimization of the enantioselective methodology is under study, less accessible alcohols should be prepared, possibly from the reduction of ketones, and tested in order to achieve higher enantioselectivities. This chiral version could be expensive due to the high ratio of chiral alcohol with respect to the substrate (1 equivalent). Heterogenous systems with supported chiral alcohols should be a solution in order to optimize the cost, and be able to scale up the reaction and become of industrial interest.

> *All life is an experiment. The more experiments you make the better.*
>
> ***Ralph Waldo Emerson***

7 Experimental part

7.1 General considerations

All reactions and manipulations were carried out under an argon atmosphere, using Schlenk-type techniques. The solvents were distilled from appropriate dehydrating reagents, and were deoxygenated before use. Bis(pinacolato)diboron was used as purchased from AllyChem. Substrates and the rest of the diboron reagents were purchased from Sigma-Aldrich or Alfa-Aesar and used as received. Deuterated solvents for routine NMR measurements were used as purchased from SDS or Cortecnet. NMR spectra were obtained on either a Varian Gemini 300 NMR, Varian Goku 400 or a Varian Mercury 400 spectrometer. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts are reported in ppm relative to tetramethylsilane, reference to the chemical shifts of residual solvent resonances. $^{11}B\{^{1}H\}$ NMR chemical shifts are reported in ppm relative to $(CH_3CH_2)_2O{\cdot}BF_3$. $^{31}P\{^{1}H\}$ NMR chemical shifts are reported in ppm relative to 85% H_3PO_4.

7.1.1 Typical procedure for the (NHC)Cu(I) mediated β-boration reaction of α,β-unsaturated esters

Bis(pinacolato)diboron (0.55 mmol) was added to a solution of the corresponding (NHC)Cu(I) catalyst (2 mol %) and base (3 mol %) in tetrahydrofuran (2 mL) under nitrogen. The solution was stirred for 5 min, and the substrate (0. 5 mmol) was then added with 2 mL of MeOH. The mixture was stirred for 6 h at room temperature. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the conversion and selectivity.

7.1.2 Typical procedure for the (NHC)Cu(I) mediated β-boration reaction of α,β-unsaturated aldehydes

With base: Bis(pinacolato)diboron (0.55 mmol) was added to a solution of the catalyst (NHC)Cu(I) (2 mol%) and base (3 mol%) in tetrahydrofurane (2 mL) under nitrogen. The solution was stirred for 5 minutes and the substrate (0.5 mmol) was then added with 2mL of MeOH. The mixture was stirred for 6 hours at room temperature. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the conversion and selectivity.

Without base: Bis(pinacolato)diboron (0.55 mmol) was added to a solution of the catalyst (IPr)CuOR (OR= OMe, O*t*Bu), (2 mol%) in tetrahydrofurane (2 mL) under nitrogen. The solution was stirred for 5 minutes and the substrate (0.5 mmol) was then added with 2mL of MeOH. The mixture was stirred for 1 hour at 70ºC. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the conversion and selectivity..

7.1.3 Typical procedure for the Pd mediated β-boration reaction of α,β-unsaturated carbonyl compounds

The dimer palladium complex (0.003 mmol) was suspended in toluene or THF (2 mL) under argon in a Schlenk tube. Bis(pinacolato)diboron (47.75 mg, 0.18 mmol) was added, the suspension was stirred for 10 min, and then Cs_2CO_3 (61 mg, 0.18 mmol) was added. A solution of α,β-unsaturated ester, ketone, aldehyde, or amide (0.125 mmol) in toluene or THF (2 mL) was then added. Finally, MeOH (1.57 mmol) and water (0.18 mmol) were added and the mixture was stirred at room temperature for 6 h. The reaction mixture were analyzed by ^{1}H NMR spectroscopy to determine the conversion and selectivity.

Typical catalytic β-boration, and subsequent Suzuki-Miyaura reaction: Bis(pinacolato)diboron (47.8 mg, 0.18 mmol) was added to a solution of the palladium dimer (2.5 mol%, 0.003 mmol Pd) and Cs_2CO_3 (61 mg, 0.18 mmol, 1.5 equiv) in THF (2 mL) under argon. The solution was stirred for 5 min, and then the α,β-unsaturated carbonyl substrate (0.12 mmol) was added followed by MeOH (63 μL, 1.57 mmol) and water (5 μL, 0.18 mmol), and stirring was continued for 6 h at room temperature. After heating at reflux, Cs_2CO_3 (122.2 mg, 0.37 mmol), the corresponding halide (0.25 mmol), and water (degassed, 0.2 mL, 10% of the solvent) were added and the reaction mixture was stirred for 24 h. After cooling, the reaction mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried over magnesium sulfate, and dried in vacuo. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the conversion and selectivity.

7.1.4 Typical procedure for the Fe assisted β-boration reaction of electrondeficient olefins:

The iron precursor (0.01 mmol) and the phosphine (0.02 mmol of phosphorus) were placed in a Schlenk tube, and dissolved in THF (2 mL) under argon. The suspension was stirred for 10 minutes and Cs_2CO_3 (0.075 mmol, when 15 mol%) was added. Afterwards, the substrate, (0.5 mmol) and bis(pinacolato)diboron (0.55 mmol) were added. Finally MeOH (100 μl, 2.5 mol) was added, and the mixture was allowed to stir at 70 °C oil bath temperature for 6h. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by G.C. to determine conversion. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to confirm the conversion previously observed by gas chromatography.

7.1.5 Typical procedure for the organocatalytic β-boration reaction of electrondeficient olefins:

without phosphine: Base, 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, (8.4 mg, 0.076 mmol) and bis(pinacolato)diboron (140 mg, 0.55 mmol) were transferred into an ovendried Schlenk tube under argon. THF (2 ml) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the diboron reagent completely. The substrate (0.5 mmol) and MeOH (100 μl, 2.5 mmol) were added, and the reaction mixture was stirred at 70 °C oil bath temperature for 24 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC/GC-MS to determine conversion, and confirm selectivity. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to confirm the conversion, and chemoselectivity previously observed by gas chromatography.

with phosphine: Phosphine (0.02 mmol), cesium carbonate (25 mg, 0.076 mmol) and bis(pinacolato)diboron (140 mg, 0.55 mmol) were transferred into an oven-dried Schlenk tube under argon. THF (2 ml) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate (0.5 mmol) and MeOH (100 μl, 2.5 mmol) were added, and the reaction mixture was stirred at 70 °C oil bath temperature for 6 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC to determine conversion. After the GC analysis the same aliquot was gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to confirm the conversion previously observed by gas chromatography.

7.1.6 Typical procedure for the organocatalytic diboration reaction of alkenes:

The base (0.076 mmol) and the diboron reagent (0.55 mmol, 140 mg if it is bis(pinacolato)diboron) were transferred into an oven-dried Schlenk tube, provided with stir bar, under argon. THF (2 ml) was added to dissolve the mixture. After that, the substrate (0.5 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at a pre-determined temperature in an oil bath for 6 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution. It was diluted with CH_2Cl_2 (1 mL) and analyzed by GC and GC-MS to determine conversion and selectivity of the reaction.

7.1.7 Typical procedure for the enantioselective organocatalytic diboration reaction of alkenes:

Cesium carbonate (0.25 mmol) and the diboron reagent (0.275 mmol) were transferred into an oven-dried Schlenk tube, provided with stir bar, under argon. DCM (1 mL) was added to dissolve the mixture. After that, the substrate (0.25 mmol) and chiral alcohol (0.5 mmol) were added, and the reaction mixture was stirred at a 45ºC in an oil bath for 16 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.1 mL was taken from the solution. It was diluted with DCM (1 mL) and analyzed by GC and GC-MS to determine conversion and products of the reaction.

7.1.8 General derivatitzations of the β-borated products in order to determine the enantiomeric excess.

Oxidation Protocol: A solution of sodium perborate (2.5 mmol) in THF-water (V:V = 1:1, 4 mL), was added to the reaction mixture. The mixture was stirred vigorously for 4 h. After this time, it was quenched with brine and then extracted with AcOEt (3 × 20 mL). The combined organic phase was dried over $MgSO_4$.[1]

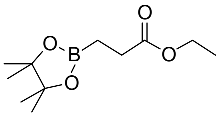
Acylation Protocol: A solution of 3 mL of acetic anhydride and 5 mL of acetic acid in 25 mL of $CHCl_3$ were added to the β-alcohol product. The reaction mixture was stirred overnight at 50 °C. The next day the mixture was extracted with AcOEt (3 × 20 mL). The organic phase was dried over $MgSO_4$. The $MgSO_4$ was filtered off, and all the volatiles were removed in vacuum.[2]

7.1.9 General derivatitzations of diborated products in order to determine the enantiomeric excess.

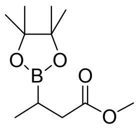
Oxidation Protocol: 1,2 diborated product was treated with 2 mL of a solution of 3M NaOH and 1 mL of a solution of 33% H_2O_2. The mixture was stirred for 4 hours. After this time, it was quenched with saturated solution of $Na_2S_2O_3$ and then extracted with AcOEt (3 x 20 mL). The organic phase was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

Acetal formation Protocol: The 1,2-diol was treated with 1 mL of 2,2'-dimetoxypropane in the presence of catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred for 30 min at 60ºC. The solution was concentrated in vacuum.[3]

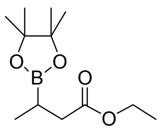
7.2 Characterization of organoboranes:



Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate:[4] ^{1}HNMR (400 MHz, $CDCl_3$): 4.12 (q, J=8 Hz, 2H), 2.4 (t, J=8 Hz, 2H), 1.27-1.22 (m, 15H), 1.01 (t, J=8 Hz, 2H).

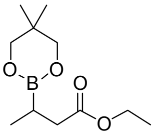


Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H NMR (300 MHz, $CDCl_3$)= δ 3.55 (s, 3 H), 2.37 (dd, *J1*= 16.4, *J2*= 7.7 Hz, 1 H), 2.32 (dd, *J1*= 16.3, *J2*= 8.7 Hz, 1 H), 1.40-1.20 (m, 1 H), 1.12 (s, 12 H), 0.95 (d, *J* = 7.5, 3H). The ee was determined on the β-alcohols by HPLC-Ms equipped with the chiral column Chiracel OD-H: 0.4 mml/min (Hexane/IPA=99.5/0.5) Rt=17.2 min (S), 22.8 min (R).

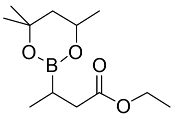


Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate:[4] ^{1}H NMR(300 MHz, $CDCl_3$) = δ 4.12 (q, *J* = 7.2 Hz, 2H), 2.43 (dd, *J* = 16.3, 7.6 Hz, 1H), 2.36 (dd, *J1*=

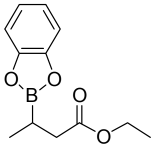
16.3, *J2*=6.6 Hz, 1H), 1.41−1.34 (m, 1H), 1.27(s, 6H), 1.25 (CH_3 overlapped, 3H), 1.22 (s, 6H), 1.00 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) = 173.9, 83.4, 60.4, 38.0, 25.1, 25.0, 15.5, 14.7, 13.8. The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 80 ºC, 27.1 psi, RT = 13.8 min (R), 14.5 min (S).



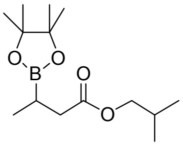
Ethyl 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)butanoate: ^{1}H NMR (400 MHz, $C_6D_3CD_3$): δ = 4.15 (q, *J*=7.2 Hz, 2H), 3.52 (s, 4H), 2.3 (m, 3H), 1.25 (t, *J*= 7.2 Hz, 2H), 0.92 (s, 6H), 0.91 (d, overlapped, 3H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 80 ºC, 27.1 psi, RT = 13.8 min (R), 14.5 min (S).



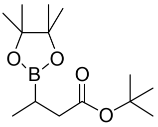
Ethyl 3-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)butanoate: ^{1}H NMR (400 MHz, $C_6D_5CD_3$): δ = 4 (q, *J* = 7.2 Hz, 2H), 3.8 (m, Bhexgly, 1H), 2.5 (dd, *J1*= 16, *J2*= 6.4 Hz, 1H), 2.41 (dd, *J1*= 16, *J2*=6.8 Hz, 1H), 1.4 (m, 1H), 1.24-1.22 (m, Bhexgly, 2H), 1.15 (d, *J*= 2.4 Hz, Bhexgly, 3H), 1.12 (s, Bhexgly, 3H), 1.09 (s, Bhexogly, 3H), 1.07 (dd, *J2* = 6.4 Hz, *J2* = 0.8 Hz, 3H), 1 (t, *J*= 6.8 Hz, 3H). ^{13}C NMR ($C_6D_5CD_3$) : δ = 173.7 (CO), 70.1, 64.5, 59.6, 45.7, 38.2, 31.3, 31.2, 27.8, 23.2, 15.7, 14.3. The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 80 ºC, 27.1 psi, RT = 13.8 min (R), 14.5 min (S).



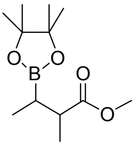
Ethyl 3-(benzo[d][1,3,2]dioxaborol-2-yl)butanoate: ^{1}H NMR (400 MHz, $C_6D_5CD_3$): δ = 6.61 (m, Bcat, 4H), 3.9 (q, *J*= 7 Hz, 2H), 2.42 (dd, *J1*=17.2, *J2*=6 Hz, 1H), 2.33 (m, 1H overlapped), 2.32 (dd, *J1*=16, *J2*=6 Hz, 1H) , 1.03 (d, *J*=7.6 Hz, 3H), 0.92 (t, *J*=7.2 Hz, 3H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 80 ºC, 27.1 psi, RT = 13.8 min (R), 14.5 min (S).



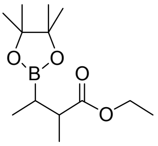
Isobutyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (m, 2H), 2.41 (dd, *J1*= 16.8, *J2*= 7.6 Hz, 1H), 2.38 (dd, *J1*= 16.8, *J2*= 7.6 Hz, 1H), 1.82 (m, 1H), 1.45 (q, *J*= 7.2 Hz, 1H), 1.26 (s, 6H), 1.21 (s, 6H), 1.02 (d, *J*= 7.2 Hz, 3H), 0.95 (d, *J*= 6.8, 6H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 70 ºC, initial time = 10 min, rate 0.5 ºC/min, final temp = 100ºC, 150 kPa, RT = 20.9 min (R), 21.4 min (S).



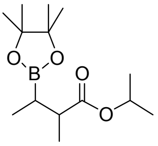
Tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate:[5] ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.34 (dd, *J1*= 16.6, *J2*= 8.7 Hz, 1 H), 2.27 (dd, *J1*= 16.6, *J2*= 7.8 Hz, 1 H), 1.36-1.25 (m, obs., 1 H), 1.25 (s, 12 H), 1.22 (s, 9 H), 0.97 (d, *J*= 7.44 Hz, 3 H).



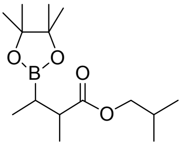
Methyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate:[6] ^{1}H RMN (400 MHz, CDCl$_3$): δ = 3.7 (s, 3H), 2.5 (m, 1H), 2.4 (m,1H), 1.3 (m, 15H), 1.1 (m, 3H), 0.9 (m, 3H). The ee was determined on the β-alcohols by HPLC-Ms equipped with the chiral column Chiracel OD-H.



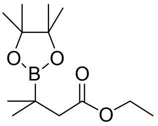
Ethyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate:[5] ^{1}H RMN (400 MHz, CDCl$_3$): δ = 4.1 (q, *J*= 7.2 Hz, 2H), 2.6 (m, 1H), 2.5 (m,1H), 1.3 (m, 15H), 1.2 (d, *J*= 7.23 Hz, H), 1.1 (d, 3H), 0.9 (m, 3H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m).



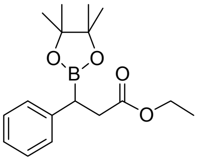
Isopropyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H RMN (400 MHz, CDCl$_3$): δ = 3.7 (m, 1H), 3.5 (d, *J*= 9.6 Hz, 2H), 2.5 (m, 1H), 2.4 (m, 1H), 1.8 (d, *J*= 6.4 Hz, 3H), 1.8 (d, *J*= 6.4 Hz, 3H), 1.3–1.1 (m, 15H), 1.1 (d, *J*= 12 Hz, 6H), 0.9 (d, *J*=12 Hz, 1H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m).



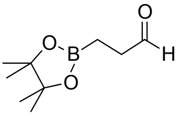
Isobutyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate: ^{1}H RMN (400 MHz, CDCl$_3$): δ = 3.7 (m, 3H), 2.5 (m, 1H), 2.4 (m,1H), 1.3 (m, 15H), 1.1 (m, 3H), 0.9 (m, 3H). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m).



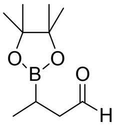
Ethyl 3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate:[6] ^{1}H NMR (400 MHz, CDCl$_3$): δ =4.16 (q, J=8.2 Hz, 2H), 2.33 (t, J=8.2 Hz, 2H), 2.18 (s, 3H), 1.25 (s, 12H), 1.90 (s, 3H), 1.00 (s, 3H)



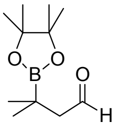
Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate:[4] ^{1}H RMN (300 MHz, CDCl$_3$): δ = 7.25-7.12 (m, 5H), 4.09 (q, J= 7.14 Hz, 2H), 2.87 (dd, J1= 16.3, J2= 9.9 Hz, 1H), 2.79-2.71 (m, 1H), 2.64 (dd, J1= 15.8, J2= 5.9 Hz, 1H), 1.26−1.16 (m, 15H). ^{13}C RMN (75 MHz, CDCl$_3$): δ = 173.4, 141.4, 128.6, 128.3, 83.7, 60.6, 37.6, 28.2, 24.9, 24.8, 14.6



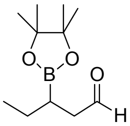
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanal:[7] ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.72 (s, 1H), 2.53 (t, J= 8 Hz, 2H), 1.22-1.14 (m, 12H), 0.91 (t, J= 8Hz, 2H)



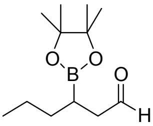
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanal: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.75 (s, 1H), 2.64-2.45 (m, 2H), 1.33 (m, 1H), 1.20 (s, 12H), 1.02 (d, J= 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 202.8, 83.3, 47.9, 25.2, 24.9, 14.4. ^{11}B NMR (96.27 MHz, CDCl$_3$): δ = 33.4. MS: M^+= 198; M^+-CH_3=183, M^+-CH_2CHO=155, M^+-CH_3-CH_2CHO= 140



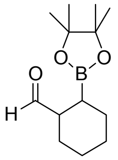
3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanal: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.72 (s, 1H), 2.45 (s, 2H), 1.23 (s, 12H), 0.98 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 203.0, 83.5, 45.2, 29.9, 29.3, 28.6, 24.7. ^{11}B NMR (96.27 MHz, CDCl$_3$): δ = (96,27 MHz, CDCl$_3$)=34.1. MS: M^+=212; M^+-CH_3=197; M^+-CH_2CHO=169; M^+-CH_3CH_2CHO=154



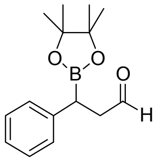
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanal: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.76 (s, 1H), 2.63-2.48 (m, 2H), 1.53-1.20 (m, 3H), 1.23 (s, 6H), 1.22 (s, 6H), 0.92 (t, J= 7.6, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 203.2, 83.4, 45.8, 24.9, 24.8, 23.6, 13.3. ^{11}B NMR (96.27 MHz, CDCl$_3$): δ = 33.2. MS: M^+=212; M^+-CH_3=197; M^+-CH_2CH_3=183; M^+-CH_2CHO=169; M^+-CH_3CH_2CHO=154



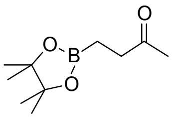
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanal: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.75 (s, 1H), 2.61-2.40 (m, 2H), 1.46-1.25 (m, 5H), 1.25 (s, 6H), 1.24 (s, 6H), 0.88 (t, *J*= 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.1, 83.4, 46.0, 32.9, 24.9, 24.8, 22.1, 11.4. ^{11}B NMR (96.27 MHz, $CDCl_3$): δ = 33.6. MS: $M^{+}=226$; $M^{+}-CH_{3}=211$; $M^{+}-CH_{2}CH_{3}=197$; $M^{+}-CH_{2}CHO=183$; $M^{+}-CH_{3}CH_{2}CHO=168$



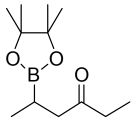
2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanecarbaldehyde: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 2.84 (dt, 1H, C*H*-CHO), 1.65-1.25 (m, 9H), 1.15 (s, 6H), 1.14 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 86.4, 43.0, 32.6, 31.8, 24.9, 24.8, 22.1, 21.4. ^{11}B NMR (96.27 MHz, $CDCl_3$): δ = 33.5



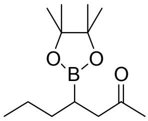
3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanal:[8] ^{1}H NMR (400 MHz, $CDCl_3$): 9.80 (s, 1H), 7.45 (dd, *J1*=6, *J2*=4 Hz, 2H), 7.25-7.21 (m, 3H), 3.05 (dd, *J1*= 20, *J2*= 12 Hz, 1H), 2.85 (dd, *J1*=20, *J2*=4 Hz, 1H), 2.71 (dd, *J1*=12, *J2*=4 Hz, 1H), 1.29-1.19 (m, 12H). The ee was determined on the β-alcohols by HPLC-Ms equipped with the chiral column Chiracel OJ: 0.5 mml/min (Hexane/IPA=99.5/0.5)



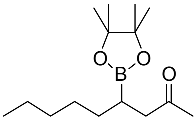
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one:[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (t, *J*=8 Hz, 2H), 2.06 (s, 3H), 1.26 (s, 12H), 0.83 (t, *J*=8 Hz,2H)



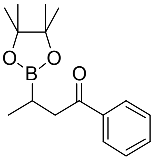
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (broad d, *J* = 6.9 Hz, 2H, CH_2), 2.38 (dq, *J1*= 7.4, *J2*= 2.2 Hz, 2H, CH_2), 1.28-1.24 (m, 1H, CH), 1.23 (s, 6H, pinacolate 2 CH_3), 1.21 (s, 6H, pinacolate 2 CH_3), 1.03 (t, *J*= 7.3, 3H, CH_3), 0.94 ppm (d, *J*= 7.5 Hz, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 211.7, 82.9, 46.2, 35.6, 25.00 24.7, 24.6, 15.0, 7.9. ^{11}B NMR: ($CDCl_3$, 128.3 MHz) δ = 34.08. MS = $[M+1]^{+}$ (227), $[M-15]^{+}$ $(-CH_{3})$ (211), $[M-58]^{+}$ $(-C_{3}H_{6}O)$ (168). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 70 ºC, 150 kPa, RT = 20.2 min,(minor) 22.4 min.(major).



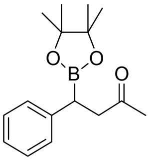
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (d, *J*= 7.0 Hz, 2H, CH_2), 2.08 (s, 3H, CH_3), 1.40-1.22 (m, 5H, 2 CH_2, CH), 1.21 (s, 6H, pinacolate 2 CH_3), 1.18 (s, 6H, pinacolate 2 CH_3), 0.84 (t, *J*= 6.8 Hz, 3H, CH_3) ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 209.3, 83.0, 45.8, 32.7, 29.8, 25.1, 24.9, 24.8, 22.2, 14.42. ^{11}B NMR: ($CDCl_3$, 128.3 MHz): δ = 33.9. MS = *[M+1]*$^+$ (241), *[M-15]*$^+$ *(-CH_3)* (225). The ee was determined on the β acyloxi product by GC-MS with the chiral column β-cyclodex (30m): 70 ºC, initial time = 10 min, rate 0.5 ºC/min, final temp = 100 ºC , 150 kPa, RT = 28.4 min. (major), 29.4 min.(minor).



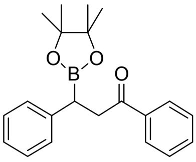
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-one: ^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (d, *J* = 7.2 Hz, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.28-1.21 (m, 9H, 4 CH_2, CH), 1.20 (s, 6H, pinacolate 2 CH_3), 1.80 (s, 6H, pinacolate 2 CH_3), 0.84 (t, *J*= 6.8 Hz, 3H, CH_3) ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 209.2, 82.9, 45.8, 31.9, 30.3, 29.6, 28.5, 24.9, 24.7, 24.6, 22.5, 14.00. ^{11}B NMR: ($CDCl_3$, 128.3 MHz): δ = 38.7. The ee was determined on the β alcohol product by GC-MS with the chiral column GTA: 70 ºC, initial time = 10 min, rate 1 ºC/min, final temp = 130ºC, 150kPa, RT = 41.5 min,(minor) 43.6 min.(major).



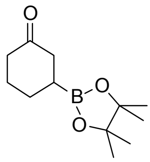
1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one:[9] ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J*= 6.9 Hz, 1H), 7.42 (t, *J*= 6.9 Hz, 2H), 3.12 (d, *J*= 6.9 Hz, 2H), 1.40 (m, 1H), 1.26 (s, 6H), 1.25 (s, 6H), 1.06 (d, *J*= 7.5 Hz, 3H). The ee was determined on the β alcohol product by GC-MS with the chiral column GTA: 70 ºC, initial time = 10 min, rate 1 ºC/min, final temp =130ºC, 150kPa, RT = 62.9 min, (R) 64.5 min.(S)



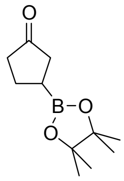
4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one:[10] ^1H NMR (400 MHz, $CDCl_3$): 7.45 (dd, *J1*= 6, *J2*= 4 Hz, 2H), 7.25-7.21 (m, 3H), 3.05 (dd, *J1*= 20, *J2*= 12Hz, 1H), 2.85 (dd, *J1*= 20, *J2*= 4 Hz, 1H), 2.71 (dd, *J1*=12, *J2*=4Hz, 1H), 1.94 (s, 3H), 1.29-1.19 (m, 12H)



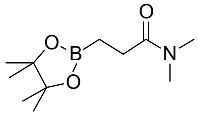
1,3-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one:[11] ^1HNMR (400 MHz, $CDCl_3$): 7.95 (dd, *J1*= 8, *J2*= 1.4Hz, 2H), 7.66-7.40 (m, 8H), 3.51 (dd, *J1*= 18, *J2*= 8 Hz, 1H), 3.35 (dd, *J1*=18, *J2*=4Hz, 1H), 2.72 (dd, *J1*=8, *J2*=4 Hz, 1H), 1.23-1.15 (m, 12H).



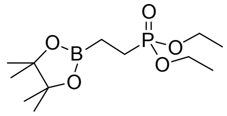
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone:[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38-2.24 (m,4H), 2.08-2.01 (m,1H), 1.88-1.83 (m,1H), 1.78-1.68 (m,1H), 1.66-1.56 (m,1H), 1.48-1.38 (m,1H), 1.22 (s, 12H, pinacolate 2 CH_3). The ee was determined on the β-borate by HPLC-Ms equipped with the chiral column Chiracel IA: 1ml/min (Hexane/IPA=99.5/0.5) RT = 14.2 min,(S) 18.4 min.(R)



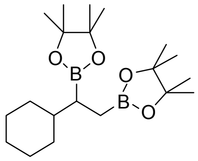
3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentanone:[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42–2.02 (m, 5H), 1.94–1.76 (m, 1H), 1.74–1.56 (m, 1H), 1.26 (s, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 221.4, 83.7, 40.4, 39.1, 25.4, 24.9.



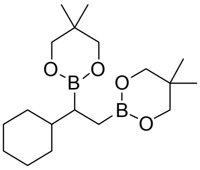
N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide:[13] ^{1}H NMR (400 MHz, $CDCl_3$): 2.98 (s, 3H), 2.93 (s, 3H), 2.45 (t, *J1*= 8Hz, 2H), 1.25-1.23 (m, 12H), 0.95 (t, *J1*=8Hz, 2H).



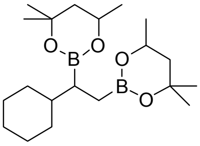
Diethyl (2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phosphonate:[14] ^{1}H NMR($CDCl_3$): δ =1.12 (m, 2H), 1.24 (s , 12H), 1.2−1.3 (m , 2H), 1.28−1.31 (t, 6H), 4.02−4.07 (q, 4H).^{13}C NMR ($CDCl_3$): δ =9.50(br), 16.27, 24.31, 24.46, 61.33, 82.81. ^{31}P($CDCl_3$): δ = 33.67. ^{11}B($CDCl_3$): δ =33.75.



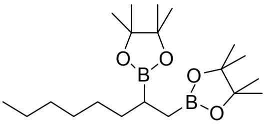
2,2'-(1-cyclohexylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):[3] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.70-1.55 (m, 10H, C_6H_{11}), 1.31 (m, 1H, C6H11), 1.23 (s, 12H, B(pin)), 1.21 (s, 12H, B(pin)), 1.20-0.97 (m, 1H, CHB(pin)), 0.80 (dd, *J1*= 16, *J2*= 4 Hz, 1H, CH_2B(pin)), 0.71 (dd, *J1* = 16, *J2* = 5.2 Hz, 1H, CH_2B(pin)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 82.76, 82.72, 41.47, 32.08, 31.96, 26.87, 26.83, 26.71, 24.96, 24.93, 24.85, 24.68.^{11}B NMR ($CDCl_3$, 128 MHz): δ = 34.76, 34.57. HRMS (ESI) m/z calculated for $C_{20}H_{38}B_2O_4$ $[M+H]^+$ = 365.3043, found: 365.3019. The ee was determined on the acetal derivated by GC-MS equipped with the chiral column β-cyclodex (30m).



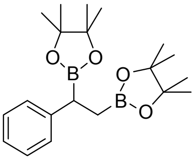
2,2'-(1-cyclohexylethane-1,2-diyl)bis(5,5-dimethyl-1,3,2-dioxaborinane): ^{1}H NMR ($CD_3C_6D_6$, 400 MHz): δ = 3.37 (s, 4H, B-(O-$(CH_2)_2$-$C(CH_3)_2$), 3.34 (s, 4H, B-(O-$(CH_2)_2$-$C(CH_3)_2$), 1.90 (m, 1H, -CH-B), 1.32 (m, 10H, C_6H_{11}), 0.89 (m, 2H, CH_2B), 0.78 (s, 6H, CH_3), 0.68 (s, 6H, CH_3).^{13}C NMR ($CD_3C_6D_6$, 100 MHz): 72.8, 72.7, 43.1, 34.0, 33.7, 33.0, 32.3, 28.6, 28.3, 22.9, 22.7, 15.3. ^{11}B NMR ($CD_3C_6D_6$, 128 MHz): δ = 30.7. HRMS (ESI) m/z calculated for $C_{18}H_{34}B_2O_4$ *[M+H]*$^+$ = 337.2721, found: 337.2729. The ee was determined on the acetal derivated by GC-MS equipped with the chiral column β-cyclodex (30m).



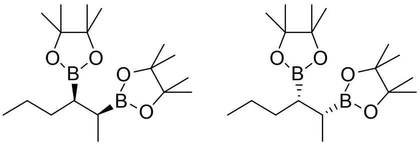
2,2'-(1-cyclohexylethane-1,2-diyl)bis(4,4,6-trimethyl-1,3,2-dioxaborinane): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.05 (m, 2H, -CHOB-), 1.66-1.60 (m, 4H, -CH_2-CH-O-B), 1.52 (m, 2H, B-CH_2, 1.35 (dt, *J1*=12.7, *J2*=2.4, 1H, C6H11-CHB-), 1.18 (s, 6H, -CH_3), 1.17 (s, 6H, -CH_3), 1.15 (d, 6H, J=6.2, -CH_3), 1.1-0.6 (m, 9H, C_6H_{10}).^{13}C NMR ($CDCl_3$, 100 MHz): δ = 70.0, 69.8, 64.2, 64.0, 46.0, 41.8, 41.7,32.5, 32.4, 32.2, 31.9, 31.5, 31.4, 28.3, 28.2, 28.1, 28.0, 27.0, 26.9, 23.4. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 30.7.HRMS (ESI) m/z calculated for $C_{20}H_{38}B_2O_4$ *[M+Na]*$^+$ = 387.2854, found: 387.2871. The ee was determined on the acetal derivated by GC-MS equipped with the chiral column β-cyclodex (30m).



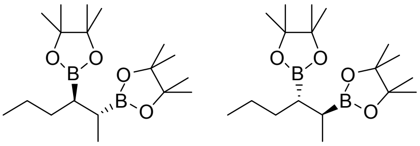
2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):[3] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (m, 1H), 1.27 (m, 8H),1.23 (s, 12H), 1.22 (s, 12H), 1.11 (m, 2H), 0.86 (t, 3H, *J*=2.4), 0.78 (dd, 3H, *J*=15.5, J=6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 82.8, 82.7, 33.9, 31.9, 29.5, 28.8, 24.9, 24.8, 24.7, 22.6, 14.1. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 35.0. HRMS (ESI) m/z calculated for $C_{20}H_{40}B_2O_4$ *[M+Na]*$^+$ = 389.3010, found: 389.3018. The ee was determined on the acetal derivated by GC-MS equipped with the chiral column β-cyclodex (30m).



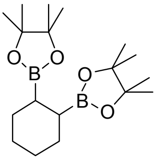
2,2'-(1-phenylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane):[3] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (d, *J*=4.0, 4H), 7.07 (m 1H), 2.5, (1H, dd, *J1*=11, *J2* =6 Hz, CH(Bpin)), 1.37 (dd, *J1*= 16, *J2* = 10.8 Hz, CHH(Bpin)), 1.2 (s, 12H, Bpin), 1.19 (s, 6H, Bpin), 1.17 (s, 6H, Bpin), 1.11 (dd, 1H, *J1*= 16, *J2*= 5.6 Hz, CHH(Bpin)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 128.1, 127.8, 124.9, 83.2, 83.0, 24.9, 24.7, 24.6, 24.5. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 35.0. HRMS (ESI) m/z calculated for $C_{20}H_{32}B_2O_4$ *[M+NH$_4$]$^+$* = 376.2830, found: 376.2830. The ee was determined on the acetal derivated by GC-MS equipped with the chiral column β-cyclodex (30m).



rac-syn -2,2'-hexane-2,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane): ^{1}H NMR ($CDCl_3$, 400 Hz): δ = 1.45 (m,1H), 1.26 (m, 2H), 1.21 (s, 12H), 1.20 (s,12H), 1.11 (m, 4H), 0. 92 (d, *J*=7.2, 3H), 0.84 (t, *J*=7.2, *J*=7.1,3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 82.9, 82.9, 32.9, 25.2, 25.0, 25.0, 22.7, 14.7, 14.1. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 35.0 (2 B). HRMS (ESI) m/z calculated for $C_{20}H_{36}B_2O_4$ *[M+Na]$^+$* = 361.2697, found: 361.2681.

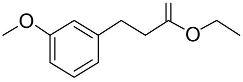


rac-anti-2,2'-hexane-2,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50 (m,2H), 1.37 (m, 2H), 1.24 (s, 12H), 1.23 (s,12H), 1.05 (m, 2H), 0.87 (t, *J*=7.6, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 82.7, 29.7, 25.1, 24.6, 22.8, 13.8. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 36.4. HRMS (ESI) m/z calculated for $C_{20}H_{36}B_2O_4$ *[M+Na]$^+$* = 361.2697, found:361.2681.

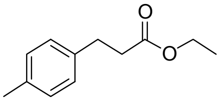


1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexane: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.67-1.50 (m, 5H), 1.48-1.34 (m, 5H), 1.23 (s, 12H, B(pin)), 1.22 (s, 12H, B(pin)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 82.96, 28.29, 27.07, 25.12, 25.04. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 34.35. HRMS (ESI) m/z calculated for $C_{18}H_{34}B_2O_4$ *[M+H]$^+$* = 337.2721, found: 337.2713.

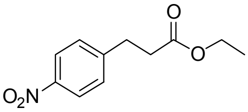
7.3 Characterization of cross coupled products



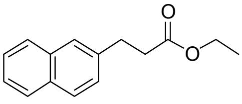
Ethyl 3-(3-methoxyphenyl)propanoate:[15] ^{1}H NMR (400 MHz, $CDCl_3$): 7.29 (s, 1H), 6.85-6.6 (m, 3H), 4.21 (q, *J1*=8.2Hz, 2H), 3.71 (s, 3H), 2.87 (t, *J*= 8Hz, 2H), 2.54 (t, *J*=8Hz, 2H), 1.21 (t, J=8.2Hz, 3H).



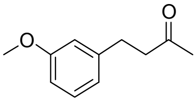
Ethyl 3-(p-tolyl)propanoate:[16] 1H NMR (400 MHz, $CDCl_3$): 7.35-7.05 (m,4H), 4.29 (q, J=8.3Hz, 2H), 2.92 (t, J=8Hz, 2H), 2.63 (t, J=8Hz, 2H), 1.05 (t, J=8.3Hz, 3H).



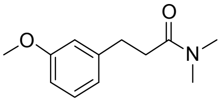
Ethyl 3-(4-nitrophenyl)propanoate:[17] 1H NMR (400 MHz, $CDCl_3$): 8.18-8.05 (m, 2H), 7.50-7.21 (m, 2H), 4.05 (q, J=8Hz, 2H), 2.99 (t, J=8Hz, 2H), 2.60 (t, J=8Hz, 2H), 1.14 (t, J=8, 3H). GC-MS: 223, 207, 195, 178, 149, 136, 119, 103, 91, 77.



Ethyl 3-(naphthalen-2-yl)propanoate:[18] 1H NMR (400 MHz, $CDCl_3$): 8.2-7.2 (m, 7H), 4.27 (q, J=8.2Hz, 2H), 3.30 (t, J=8Hz, 2H), 2.87 (t, J=8Hz, 2H), 1.25 (t, J=8.2Hz, 3H).



4-(3-methoxyphenyl)butan-2-one:[19] 1H NMR (400 MHz, CDCl3): 7.35 (s, 1H), 6.91-6.7 (m, 3H), 3.87 (s, 3H), 2.94 (t, J=8Hz, 2H), 2.62 (t, J=8Hz, 2H), 2.18 (s, 3H).



3-(3-methoxyphenyl)-N,N-dimethylpropanamide: 1H NMR (400 MHz, $CDCl_3$): 7.25 (s, 1H), 7.20 (t, J=7.6Hz, 1H), 6.80-6.70 (m, 2H), 3.7 (s, 3H, - OCH3), 2.9 (m, 8H), 2.6 (t, J=7.2Hz, 2H, Ar-CH_2- CH_2-) 13C NMR: 172, (CO) 159 (Carom-OMe),143 (Carom), 129 (Carom), 120 (Carom), 114 (Carom), 111 (Carom), 55 (CH_2-CH_2-$N(CH_3)_2$), 37 (- OCH_3), 35 (-$N(CH_3)_2$), 29 (CH_2-CH_2-$N(CH_3)_2$) GS-MS: 177, 133, 120, 105, 91, 72, 58, 45.

7.4 References

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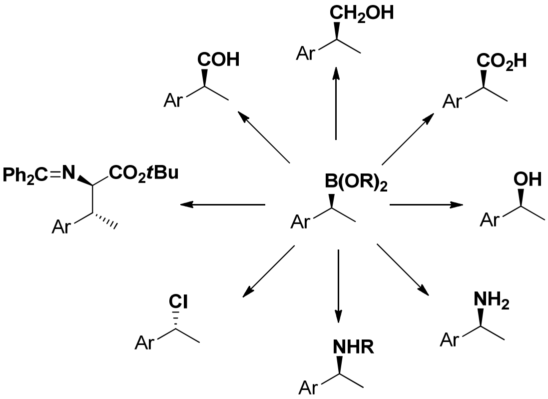
There is nothing more dangerous than no take risks. / No hi ha res més perillós que no arriscar-se.

Pep Guardiola

8 Summary / Resum

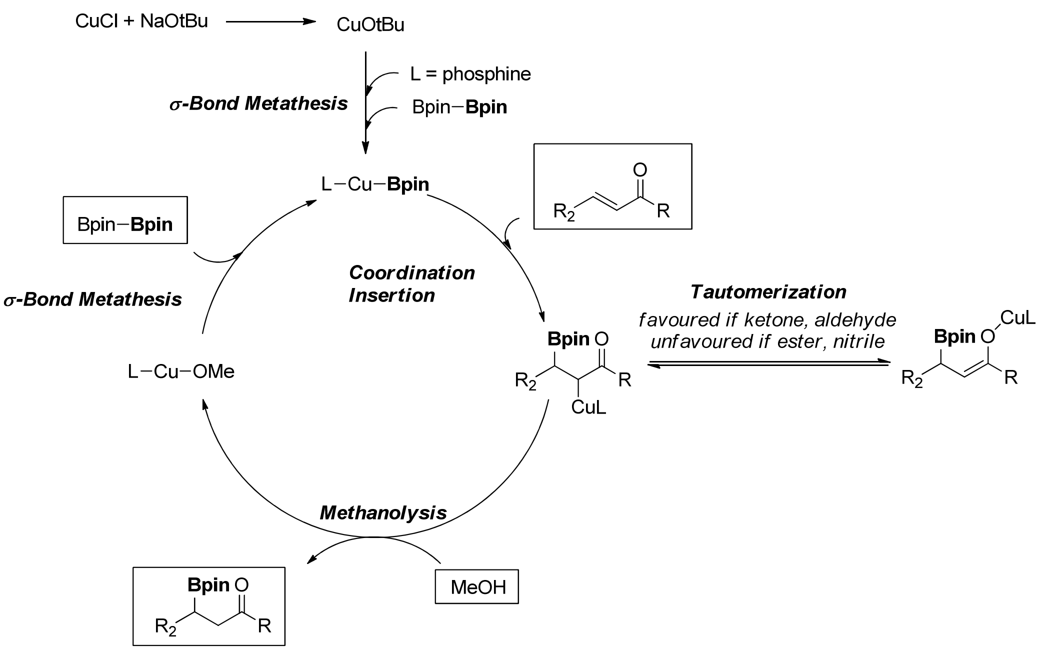
The organoborane products are highly used in a broad number of fields, from their use in medicine as a ^{10}B carrier for neutron capture therapy, or other molecules with biological activity, to their use as functional molecules such as polymers. We focused special attention to the use of organoborane molecules as intermediates in the synthesis of high value products (Scheme 8.1).



Scheme 8.1: General derivatitzation of the C-B

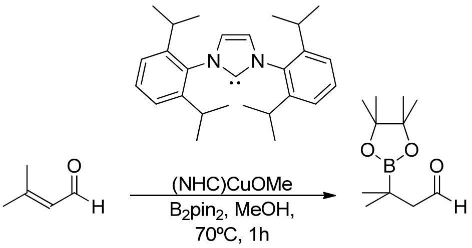
The main topic of this thesis covers the development of synthetic methods to obtain organoboranes in an efficient way. Particular efforts have been devoted to the synthesis of β-boryl carbonyl compounds, as "synthons" for the synthesis of difunctionalized molecules. We have studied the boron addition reaction to unsaturated molecules *via* two different strategies: the metal catalyzed boron addition and the metal free version. Special emphasis has been dedicated to the asymmetric approaches.

The β-boration reaction can be considered a relatively young reaction. It was performed for the first time in 1997 by Marder and coworkers[1] using platinum as a catalyst. Later on Kabalka, Hosomi and Miyaura developed new catalytic systems with Rh[2] and Cu[3]. It's no until 2006, that Yun and coworkers[4] introduced the application of alcohol as additive, which has been proved to be highly beneficial in terms of activity. These authors also developed the first chiral version of this reaction by copper complexes modified with chiral phosphines (Scheme 8.2).[5]



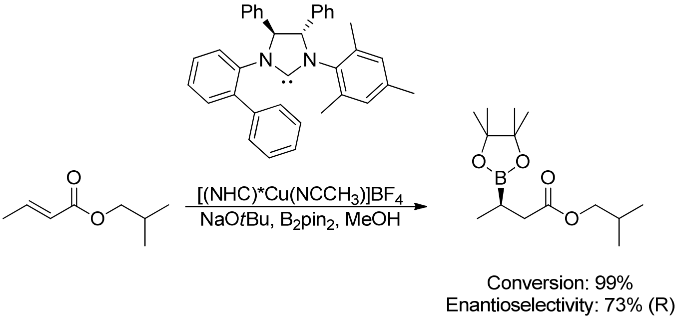
Scheme 8.2: General and accepted mechanism for the copper mediated β-boration reaction

Our first objective was the development of the copper catalyzed β-boration of the most challenging substrates: the α,β-unsaturates aldehydes. We proved that alkoxi-copper(I) complexes modified with N-heterocyclic carbene ligands, were the key catalyst precursors for the selective β-boration of aldehydes and their application avoided the use of base in the reaction media (Scheme 8.3).



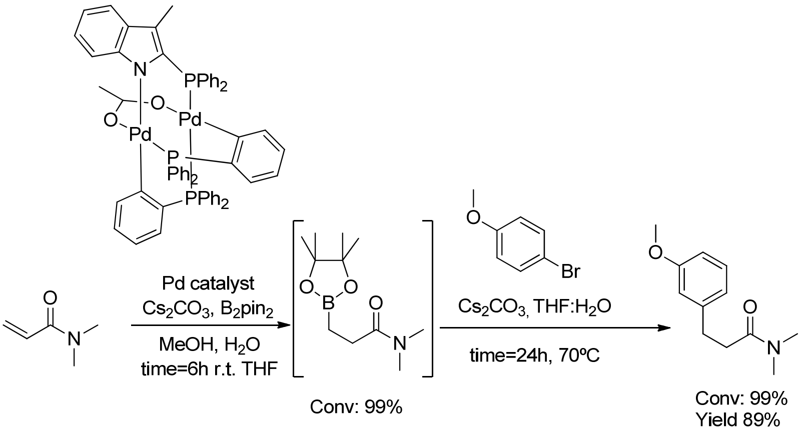
Scheme 8.3: (NHC)Cu(I) mediated selective β-boration of α,β-unsaturated aldehydes

The second objective was to explore chiral N-heterocyclic carbene ligands in the copper mediated asymmetric β-boration of α,β-unsaturated esters. It represented the first attempt to use other chiral ligands than chiral phosphines to induce asymmetry in the β-boration reaction. We observed a trend with the bulkiness of the ester moiety and we obtained excellent conversions and enantioselectivities (up to 73% of ee) in the β-boration of isobutyl crotonate (Scheme 8.4). At that time, it was the second highest enantomeric exces in the literature. Also, we tested the reaction with the cinnamaldehyd obtaining enantioselectivities up to 40%ee being since then the best result reported in the literature for the asymmetric β-boration of α,β-unsaturated adehydes.



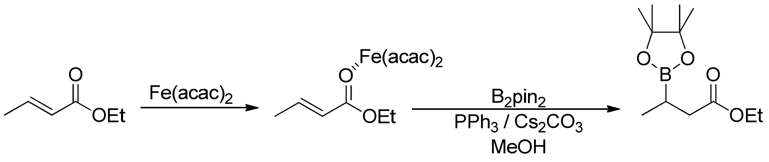
Scheme 8.4: (NHC)*Cu(I) mediated enantioselective β-boration reaction of α,β-unsaturated esters

Simultaneously, our group studied the palladium mediated asymmetric β-boration reaction with excellent results in terms of activity and enantioselectivity.[6] The use of palladium catalyst provided the opportunity to conduct consecutive boron addition reactions and cross-coupling reactions with the same catalytic system. We used palladium complexes that catalyzed, in situ, the β-boration of activatied olefins and the subsequent arylation. This method was efficient particularly for α,β-unsaturated amides (Scheme 8.5), avoiding any isolation of intermediates or use of an extra amount of catalyst.



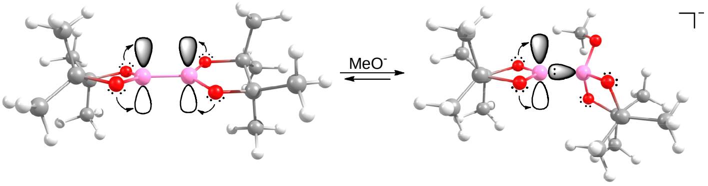
Scheme 8.5: Pd complexes mediated tandem reaction: β-boration/arylation reaction in one pot system

After palladium and copper, we focused our efforts on a cheaper and environmentally friendly transition metal: iron. In our study, we concluded that iron might act as a Lewis acid assisting the β-boration reaction by interaction with the carbonyl moiety (Scheme 8.6). We obtained total conversions in only 6h. Chiral phosphines were explored to induce asymmetry, but only moderate enantiomeric excesses were achieved at room temperature.



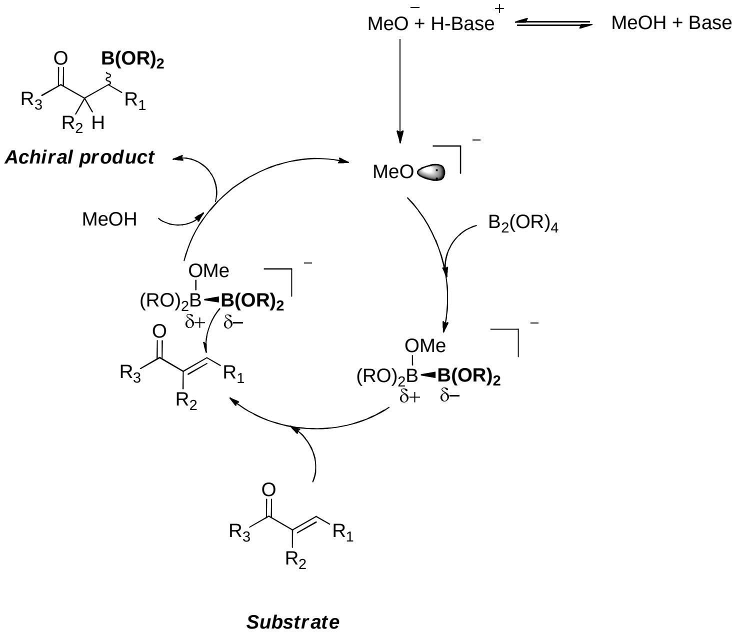
Scheme 8.6: Iron assisted β-boration reaction

To clearly understand the iron/phosphine assisted β-boration reaction we performed the reaction without iron source. To our surprise, using only base and methanol, 45% of the α,β-unsaturated ester was converted into the β-borated product. This initiated a new scientific adventure: the metal free catalytic β-boration reaction. Verkade's base showed a higher activity than the majority of the inorganic bases but closer than cesium carbonate and sodium *tert*-butoxide. NMR studies and theoretical calculations concluded that the base and the alcohol formed the corresponding alkoxide, which could interact with the diboron reagent, forming a Lewis acid-base adduct and polarizing the B-B bond (Scheme 8.7).



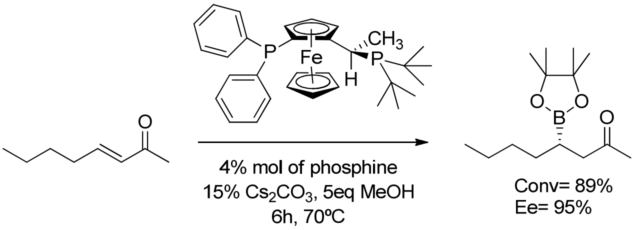
Scheme 8.7: Equilibrium in the formation of Lewis acid-base adduct

Theoretical calculation elucidated the catalytic cycle concluding that the sp^2 moiety in [MeO→Bpin-Bpin]$^-$ had a nucleophilic character and could attack the activated olefin to form the β-borated product (Scheme 8.8). This methodology allowed the activation of the most common and commercially available diboron reagents, and the β-boration of a large scope of activated olefins, working at 70ºC.



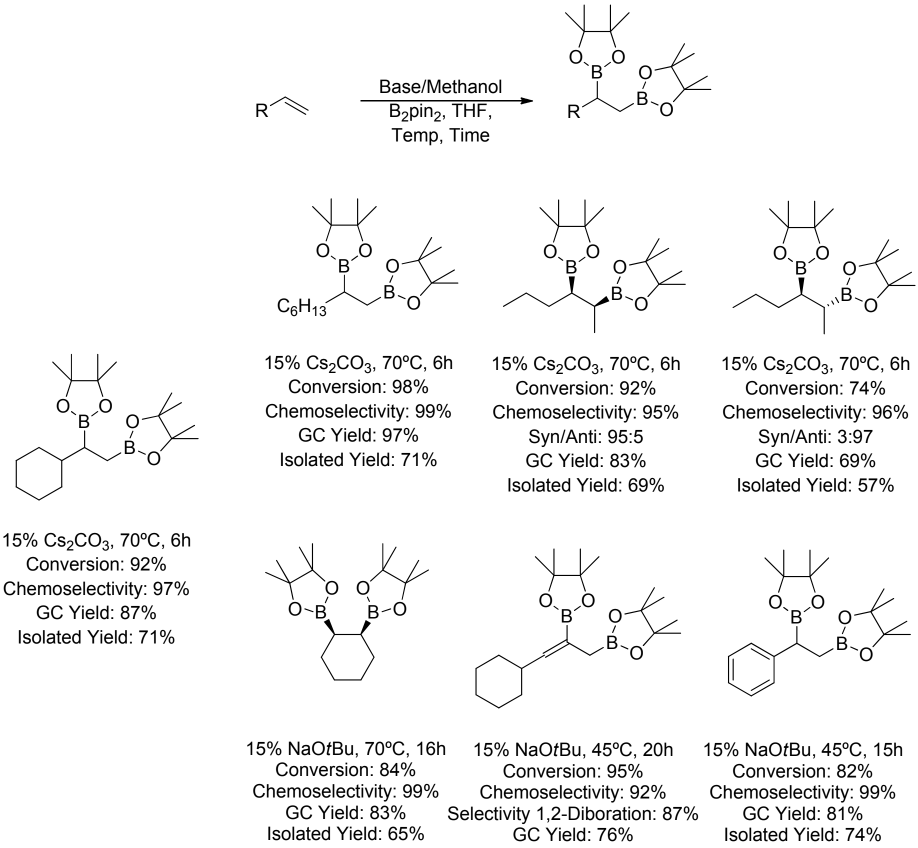
Scheme 8.8: Catalytic cycle of organocatalytic β-boration reaction

Motivated to know more about the role of the phosphine, in the organocatalytic β-boration reaction, we observed that the addition of PR_3 increased substantially the rate of the β-boration reaction. Even more importantly, the use of chiral phosphine induced asymmetry in the organocatalytic β-boration reaction with enantiomeric excesses up to 95% (Scheme 8.9).



Scheme 8.9: Enantioselective organocatalytic β-boration

Finally we have found that the adduct [MeO→Bpin-Bpin]$^-$ is capable of adding the nucleophilic Bpin moiety to non-activated olefins. Surprisingly, in addition to the hydroborated product, the diborated one was also observed. Even more surprisingly, when simple and non-activated olefins were tested as substrates, complete and selective diboration was only observed. In contrast with the usual metal mediated diboration reaction, the organocatalytic approach is easy, selective and cheap, and could be extended to the most common non-activated alkenes (Scheme 8.10).



15% Cs_2CO_3, 70ºC, 6h
Conversion: 98%
Chemoselectivity: 99%
GC Yield: 97%
Isolated Yield: 71%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 95%
Syn/Anti: 95:5
GC Yield: 83%
Isolated Yield: 69%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 74%
Chemoselectivity: 96%
Syn/Anti: 3:97
GC Yield: 69%
Isolated Yield: 57%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 97%
GC Yield: 87%
Isolated Yield: 71%

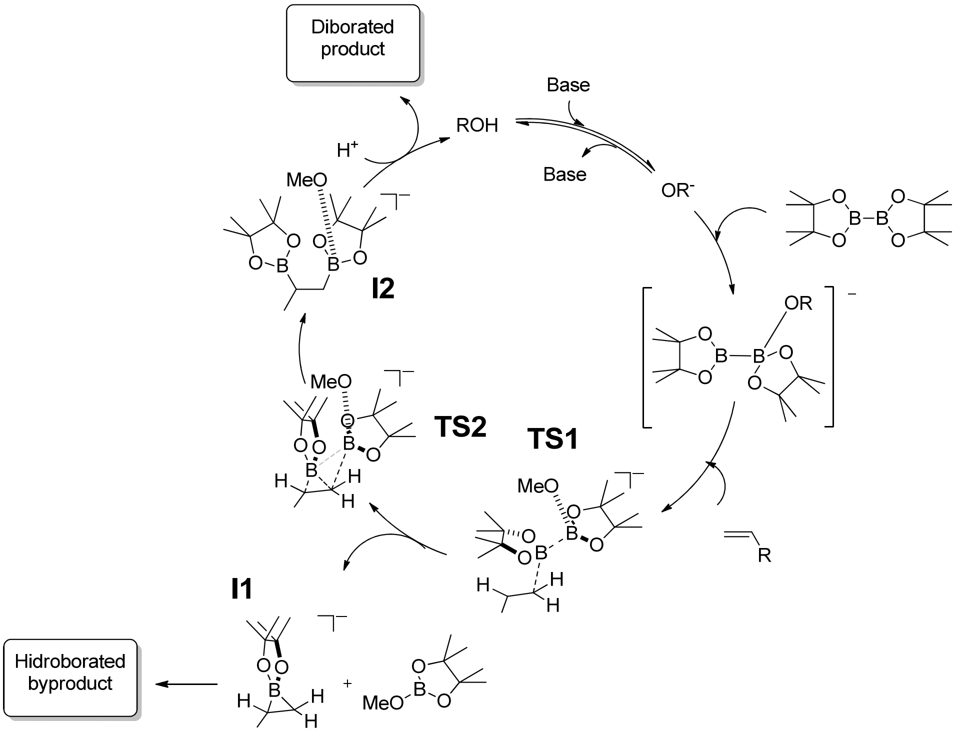
15% NaO*t*Bu, 70ºC, 16h
Conversion: 84%
Chemoselectivity: 99%
GC Yield: 83%
Isolated Yield: 65%

15% NaO*t*Bu, 45ºC, 20h
Conversion: 95%
Chemoselectivity: 92%
Selectivity 1,2-Diboration: 87%
GC Yield: 76%

15% NaO*t*Bu, 45ºC, 15h
Conversion: 82%
Chemoselectivity: 99%
GC Yield: 81%
Isolated Yield: 74%

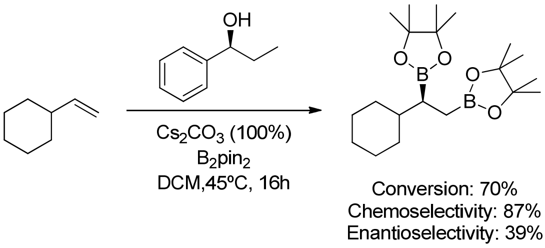
Scheme 8.10: Scope of organocatalytic diboration reaction

From the mechanistic point of view, two transition states could explain the formation of the diborated product and the hydroborated byproduct. Hence the reaction between the reaction partners seems to start by the nucleophilic attack of the B(sp^2) moiety to the less hindered carbon of the olefin providing the first transition state (TS1). Upon the nucleophilic attack, while the B(sp^2)-C_1 bond is being formed, the B-B bond is weaking, and the electrondensity is increasing on C_2. Nucleophilic attack from C_2 towards the Bpin moiety can conduct to the formation of I1 and TS2. If the electronic and steric effects stabilize the C_1-B(sp)^2 interaction, the I1 is formed towards the hydroborated byproduct. Another hand, if C_1 attacks to the Bpin(OMe) moiety, TS2 will be formed towards the formation of the diborated product (Scheme 8.11).



Scheme 8.11: Suggested catalytic cycle of organocatalytic diboration

The last goal involved the attempt to perform the organocatalytic diboration with asymmetric induction. Since alcohols are cheap, commercially available and most of them come from natural products, our approach consisted iof the use of chiral alcohols in order to form a chiral adduct [*RO→Bpin-Bpin]$^-$. Chiral commercially available alcohols were applied, but under optimized conditions enantioselectivies obtained were moderate not exceeding than 42% (Scheme 8.12).



Scheme 8.12: Approach to be enantioselective organocatalytic diboration reaction

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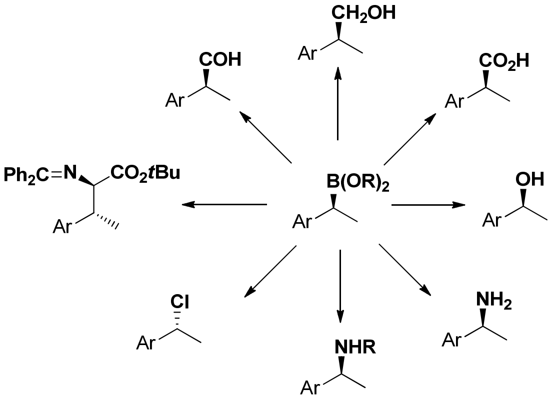
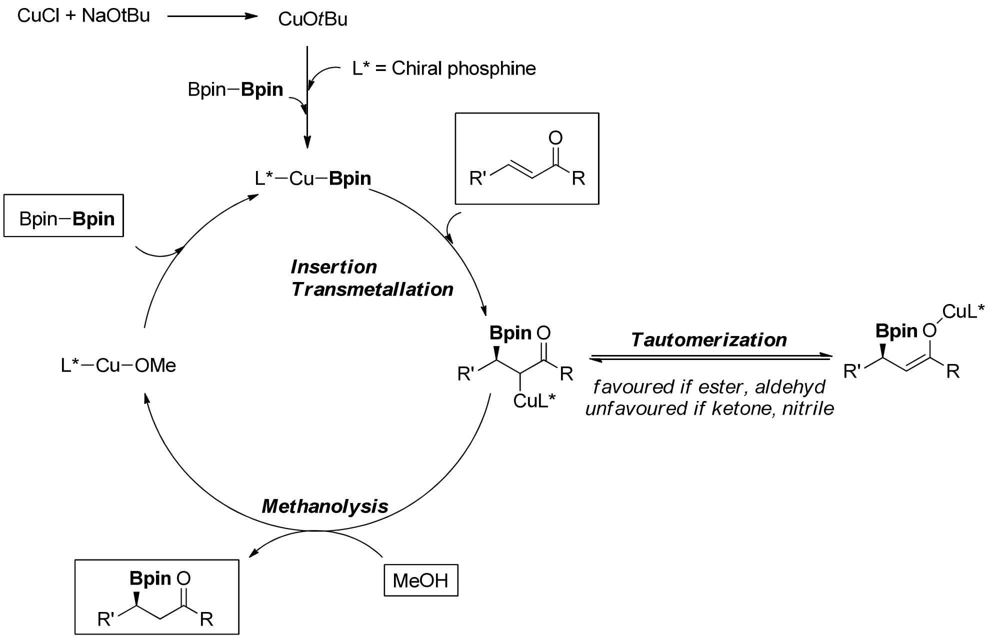
Els compostos organoborats són altament utilitzats en un extens nombre de camps, des de la medicina, en la teràpia de captura neutrònica en bor o altres molècules amb activitat biològica, fins a l'ús de molècules funcionals com els polímers. Nosaltres hem centrat la nostra atenció a l'ús dels compostos organoborats com intermedis de síntesis per a productes d'alt valor afegit (Esquema 8.1).



Esquema 8.1: Derivatitzacions generals de l'enllaç C-B

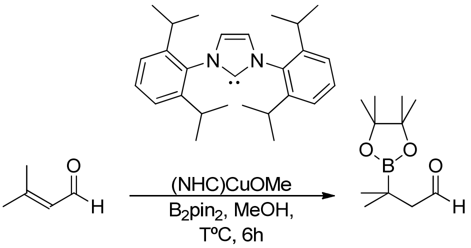
El tema principal d'aquesta tesis és el desenvolupament de noves metodologies sintètiques per a l'obtenció de compostos organoborats de manera eficient. Ens hem centrat en la síntesis de compostos carbonílics β-borats, com a sintons per a la síntesis de molècules difuncionals. Hem estudiat l'addició de bor a molècules insaturades des de dos estratègies diferents: l'addició catalítica de bor mitjançant metalls de transició i l'addició de bor sense metall. Sempre ficant especial èmfasis en la versió quiral de la reacció.

La reacció de β-boració es pot considerar una reacció relativament jove. La van realitzar la per primera vegada Marder i col·laboradors[1] utilitzant platí com a catalitzador. Després Kabalka, Hosomi i Miyaura van desenvolupar nous sistemes catalítics amb Rh[2] i Cu[3]. Però no és fins el 2006, quan Yun i col·laboradors[4] van introduir un dels majors avenços en la reacció, que és la introducció de l'alcohol com a additiu. L'ús de l'alcohol incrementa la velocitat de reacció i permet les primeres versions quirals de la reacció (Esquema 8.2).[5]



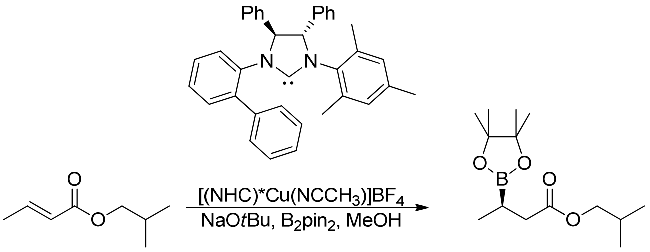
Esquema 8.2: Mecanisme general i acceptat per a la reacció de β-boració catalítica catalitzada per coure.

El nostre primer objectiu va ser el desenvolupament de la reacció de β-boració amb coure amb un dels substrats més complicats : els aldehids α,β-insaturats. Nosaltres hem demostrat que els alcòxids de coure modificats amb lligands N-heterociclic carbens, són claus per a la β-boració selectiva d'aldehids evitant l'ús de la base en el medi de reacció.



Esquema 8.3: β-boració catalítica i selectiva dels aldehids α,β-insaturats mitjançant (NHC)Cu(I)

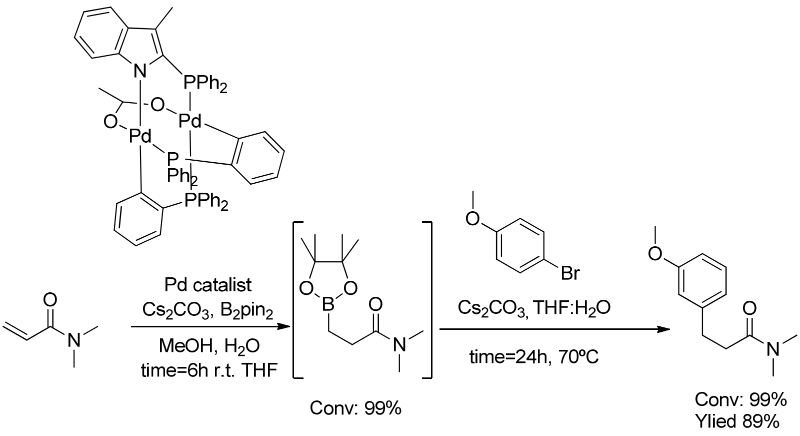
El segon objectiu va ser explorar els lligands carbens N-heterocíclics en la β-boració asimètrica d'esters α,β-insaturats. Aquesta va ser la primera vegada que es va utilitzar uns altres lligands quirals diferents de a les vegada que es va utilitzar uns altres lligands quirals diferents de a les fosfines per a introduir quiralitat en la reacció de β-boració. Nosaltres hem observat una tendència de l'enantioselectivitat amb la grandària del grup èster, a part hem obtingut conversions excel·lents i enantioselectivitats fins a 73% en la β-boració del crotonat d'isobutil (Esquema 8.4). En aquell moment, aquest resultat era el segon excés enantiomèric més alt de la literatura. També vam provar la reacció amb el cinamaldehid obtenint enantioselectivitats fins al 40%, seguint aquest resultat el més alt reportat fins a dia d'avui a la literatura per als aldehids α,β-insaturats.



Conversion: 99%
Enantioselectivity: 73% (R)

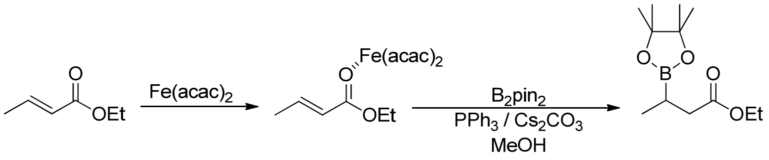
Esquema 8.4: β-boració enantioselecitva d'èsters α,β-insaturats mitjançant (NHC)*Cu

Al mateix temps, en el nostre grup, havia estudiat la reacció de β-boració asimètrica amb pal·ladi, obtenint excel·lents resultats en termes d' activitat i enantioselectivitat.[6] L'ús dels catalitzadors de pal·ladi van obrir una nova perspectiva per a realitzar dos reaccions consecutives, la β-boració i el creuament creuat, amb el mateix sistema catalític. Amb aquesta idea en ment, utilitzant complexos de pal·ladi vam aconseguir realitzar, in situ, la β-boració i arilació. Aquesta seqüència va ser particularment eficient en el cas de les amides α,β-insaturades (Esquema 8.5) sense haver d' aïllar els intermedis de reacció o utilitzar un excés de catalitzador.



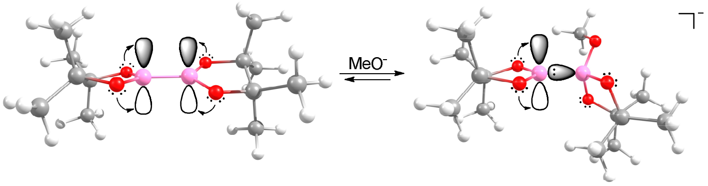
Esquema 8.5: Reacció de β-boració/arilació catalítica en un únic sistema mitjançant catalitzadors de pal·ladi

Després del pal·ladi i coure, vam centrar els nostres esforços amb el ferro, un metall de transició més barat i sostenible. En el nostre intent, vam concloure que el ferro podria actuar com a àcid de Lewis assistint la reacció de β-boració catalítica mitjançant una interacció amb el carbonil (Esquema 8.6). Nosaltres vam aconseguir conversions totals en tan sols 6h. També vam explorar les fosfines quirals, per a intentar introduir asimetria, però només excessos enantiomèrics moderats es van aconseguir a temperatura ambient.



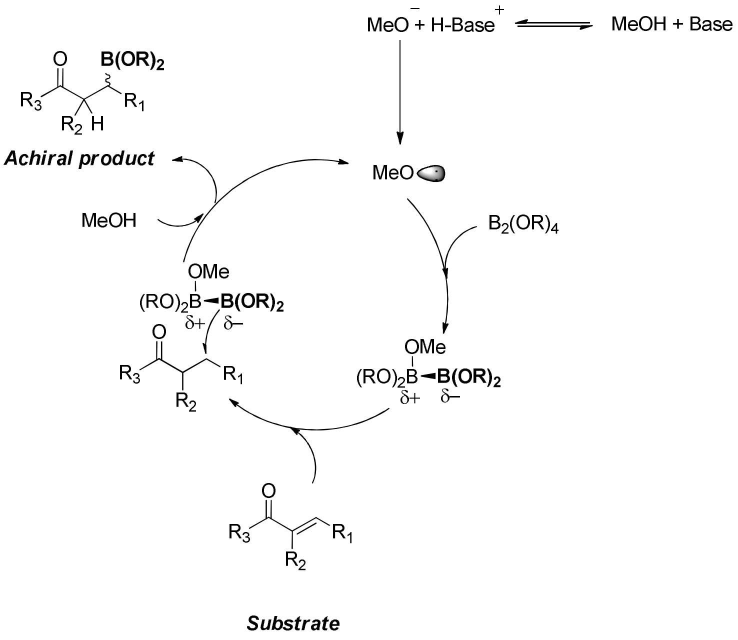
Esquema 8.6: Reacció β-boració mitjançant ferro com a catalitzador

Per a aclarir i entendre el sistema de ferro/fosfina de la reacció de β-boració catalítica vam realitzar la reacció sense ferro. La nostra sorpresa es que, utilitzant tan sols la base i el metanol, convertia el crotonat d'etil en un 45%. Això va iniciar una nova aventura científica en la qual la reacció de β-boració catalítica es podria realitzar sense metall de transició. La base orgànica, Verkade, va resultar ser superior que la majoria de les bases inorgàniques, tot i això propera al carbonat de cesi i del *tert*-butoxi de sodi. Els estudis d' RMN i els càlculs teòrics van permetre concloure que la barreja de la base i l'alcohol permet la formació de l'alcòxid i aquest és capaç d'interaccionar amb el diborà, formant un adducte àcid-base de Lewis i polaritzant l'enllaç B-B (Esquema 8.7).



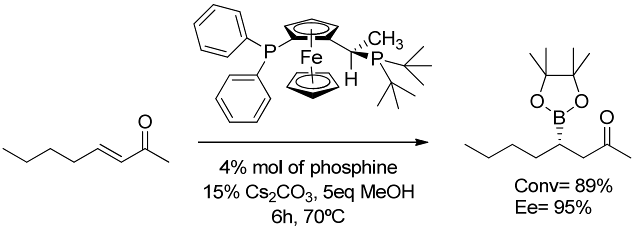
Esquema 8.7: Equilibri en la formació de l'adducte àcid-base de Lewis

Els càlculs teòrics van elucidar el cicle catalític i van concluir que l'espècie sp^2 de l'adducte $[MeO \rightarrow Bpin\text{-}Bpin]^-$ té un caràcter nucleòfil i pot atacar a l' olefina activada per a formar el producte de β-boració. Aquesta metodologia permet l'activació dels diborans més comuns i disponibles comercialment i la β-boració amb un rang de substrats molt gran.



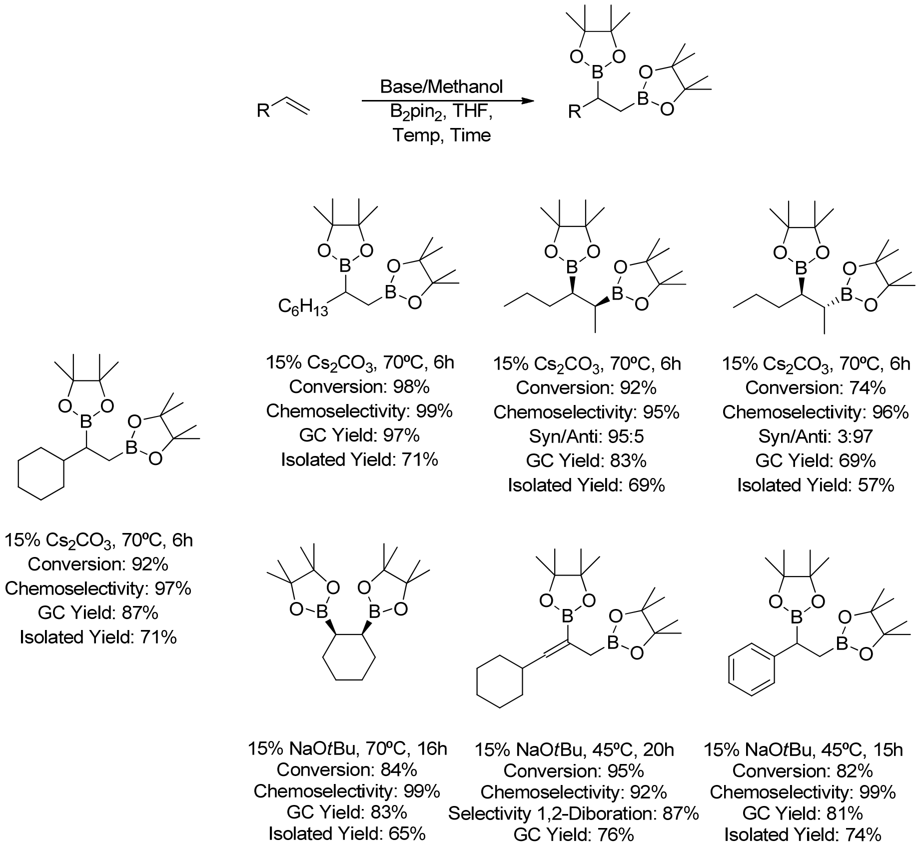
Esquema 8.8: Cicle catalític de la reacció de β-boració

Motivats per saber més sobre el rol de la fosfina, en la β-boració organocatalítica, vam observar que quan addicionàvem fosfina de forma catalítica incrementàvem substancialment la velocitat de reacció de la β-boració. A més a més, l' introducció d'una fosfina quiral permet l' inducció enantiomèrica en la β-boració organocatalítica, obtenint excessos enantomèrics fins el 95%.



Esquema 8.9: β-boració enantioselectiva organocatalitica

Finalment, hem trobat que l'adducte [MeO→Bpin-Bpin]$^-$ pot transmetre el Bpin nucleòfilic a les olefines no activades. En quest context, vam pensar que els carbonils de les olefines electrodeficients conjugades podien ser substituïdes per un altre grup electrodeficient, com un benzil, per obtenir el producte hidroborat. Sorprenentment, a part del producte de hidroboració, el producte de diboració va ser observat. Encara més sorprenentment, quan olefines simples i sense activar van ser utilitzades com a substrats, el producte de diboració es va obtenir de forma total i selectiva. A diferència amb la reacció de diboració mitjançant els metalls de transició, l'enfocament organocatalític és simple, selectiu i econòmic i poc ser estès a els més comuns i simples alquens (Esquema 8.10).



15% Cs_2CO_3, 70ºC, 6h
Conversion: 98%
Chemoselectivity: 99%
GC Yield: 97%
Isolated Yield: 71%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 95%
Syn/Anti: 95:5
GC Yield: 83%
Isolated Yield: 69%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 74%
Chemoselectivity: 96%
Syn/Anti: 3:97
GC Yield: 69%
Isolated Yield: 57%

15% Cs_2CO_3, 70ºC, 6h
Conversion: 92%
Chemoselectivity: 97%
GC Yield: 87%
Isolated Yield: 71%

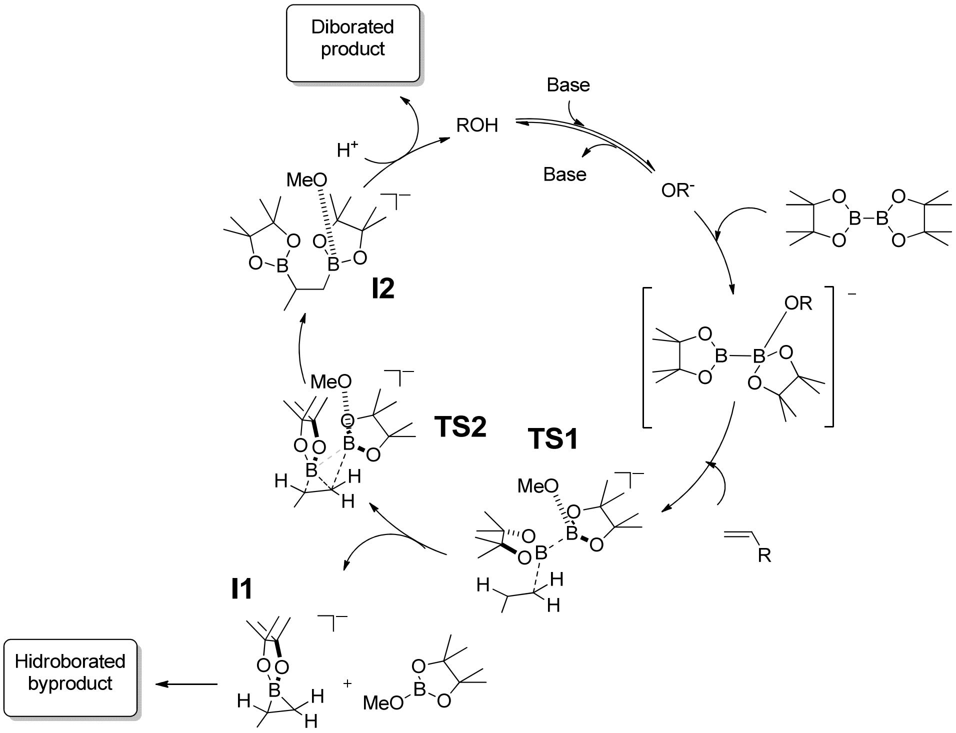
15% NaO*t*Bu, 70ºC, 16h
Conversion: 84%
Chemoselectivity: 99%
GC Yield: 83%
Isolated Yield: 65%

15% NaO*t*Bu, 45ºC, 20h
Conversion: 95%
Chemoselectivity: 92%
Selectivity 1,2-Diboration: 87%
GC Yield: 76%

15% NaO*t*Bu, 45ºC, 15h
Conversion: 82%
Chemoselectivity: 99%
GC Yield: 81%
Isolated Yield: 74%

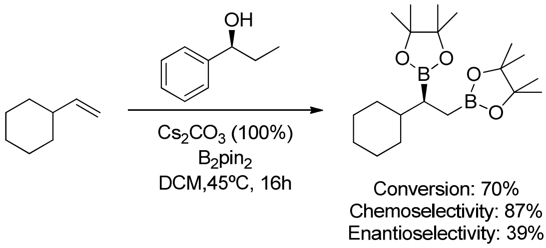
Esquema 8.10: Extensió de la reacció de diboració organocatalítica

Des del punt de vista mecanístic, dos estats de transició poden explicar la formació del producte de diboració i del subproducte d'hidroboració. La reactivitat entre els reactius sembla que comença amb un atac del boril sp^2 de l'adducte sobre el carboni menys impedit del doble enllaç, donant el primer estat de transició (TS1).Després d'això, l'alta densitat electrònica concentrada en el carboni intern permet un atac nucleòfil d'aquest al boril més proper. Immediatament després, el C1 del substrat realitza un atac nucleòfil sobre el metoxi-boryl electrofílic, donant el segon estat de transició (TS2) que acaba donant el producte de diboració. Si, els efectes electrònics o estèrics fan que el TS1 s'estabilitzi, s'afavoreix l'aparició de l'intermedi 1 (I1) que acaba donant el subproducte de diboració (Esquema 8.11).



Esquema 8.11: Cicle catalytic sugerit per a la diboració organocatalítica

L'última troballa ha estat realitzar la diboració organocatalítica de forma enantioselectiva. Els alcohols són barats, estan disponibles comercialment i la majoria venen de productes naturals, el nostre intent resideix en l'ús d'acohols quirals per obtenir l'adducte quiral [*RO→Bpin-Bpin]$^{-}$. Alcohols quirals derivats de productes naturals, d'esquelets de famosos lligands, o petits alcohols commercials van compondre una petita llibreria d'alcohols quirals, malgrat els nostres esfoços, en les condicions òptimes només vam obtenir baixes enantioselectivitats entre el 39-42% (Esquema 8.12).



Esquema 8.12: Intent de reacció enantioselectiva de diboració organocatalítica

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[1] Y. G. Lawson, M. J. Gerald Lesley, T. B. Marder, N. C. Norman, C. R. Rice *Chem. Commun*. **1997**, 2051

[2] G. W. Kabalka, B. C. Das, S. Das *Tetrahedron Letters* **2002**, *43,* 2323

[3] K. Takahashi, T. Isiyama, N. Miyaura *J. Organomet. Chem.* **2001**, *625*, 47; H. Ito, H. Yamaka, J. Tateiwa, A. Hosomi *Tet. Lett.* **2000**, *41*, 6821

[4] S. Mun, J.-E. Lee, J. Yun *Org. Lett.* **2006***, 8,* 4887

[5] J.-E. Lee, J. Yun *Angew. Chem. Int. Ed.* **2008**, *47*, 145

[6] V. Lillo, M. J. Geier, S. A. Westcott, E. Fernández, *Org. Biomol. Chem.* **2009**, *7*, 4674

In basketball – as in life – true joy comes from being fully present in each and every moment, not just when things are going your way.

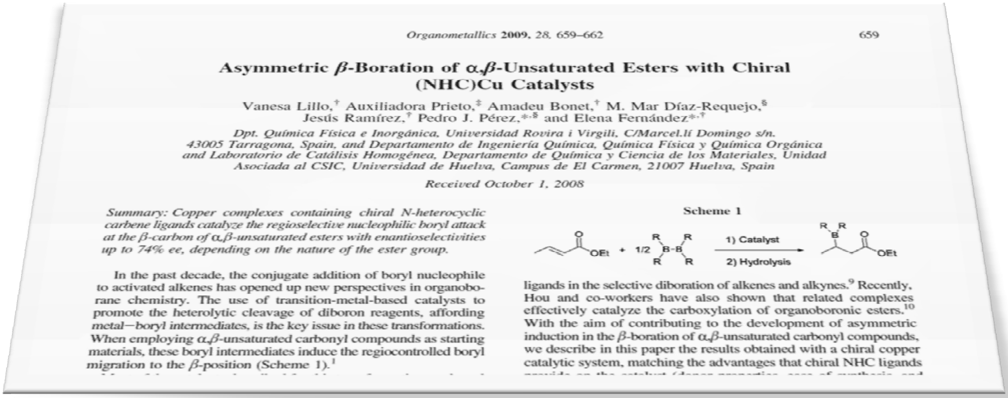
Phil Jackson

9 Appendix

9.1 Publicacions

9.1.1 Primary Publications

1. Asymmetric β-Boration of α,β–Unsaturated Esters with Chiral (NHC)Cu Catalysts; V. Lillo, A. Prieto, **A. Bonet**, M.M. Díaz Requejo, J. Ramírez, P. J. Pérez, E. Fernandez. *Organometallics*, **2009**, *28*, 659.



Organometallics **2009**, *28*, 659–662 659

Asymmetric *β*-Boration of α,*β*-Unsaturated Esters with Chiral (NHC)Cu Catalysts

Vanesa Lillo,[†] Auxiliadora Prieto,[‡] Amadeu Bonet,[†] M. Mar Díaz-Requejo,[§]
Jesús Ramírez,[†] Pedro J. Pérez,[*,§] and Elena Fernández[*,†]

Dpt. Química Física e Inorgánica, Universidad Rovira i Virgili, C/Marcel.lí Domingo s/n. 43005 Tarragona, Spain, and Departamento de Ingeniería Química, Química Física y Química Orgánica and Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Universidad de Huelva, Campus de El Carmen, 21007 Huelva, Spain

Received October 1, 2008

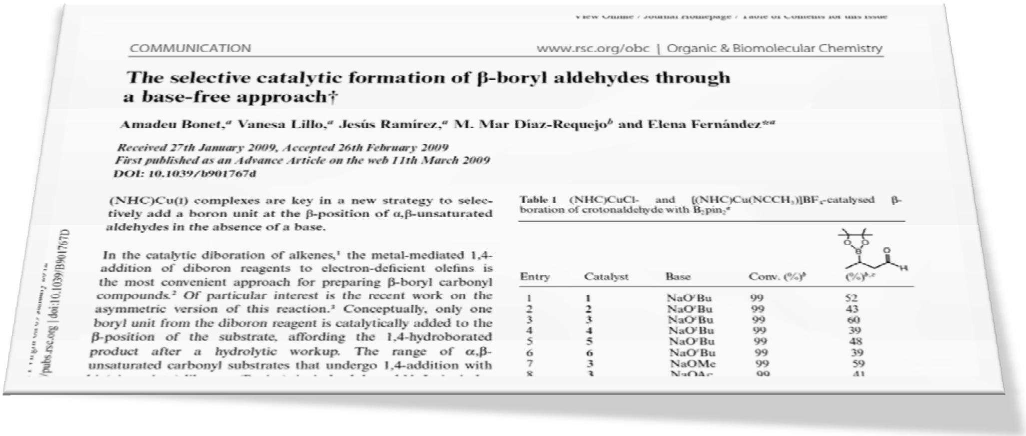
Summary: Copper complexes containing chiral N-heterocyclic carbene ligands catalyze the regioselective nucleophilic boryl attack at the β-carbon of α,β-unsaturated esters with enantioselectivities up to 74% ee, depending on the nature of the ester group.

In the past decade, the conjugate addition of boryl nucleophile to activated alkenes has opened up new perspectives in organoborane chemistry. The use of transition-metal-based catalysts to promote the heterolytic cleavage of diboron reagents, affording metal–boryl intermediates, is the key issue in these transformations. When employing α,β-unsaturated carbonyl compounds as starting materials, these boryl intermediates induce the regiocontrolled boryl migration to the β-position (Scheme 1).[1]

Scheme 1

ligands in the selective diboration of alkenes and alkynes.[9] Recently, Hou and co-workers have also shown that related complexes effectively catalyze the carboxylation of organoboronic esters.[10] With the aim of contributing to the development of asymmetric induction in the β-boration of α,β-unsaturated carbonyl compounds, we describe in this paper the results obtained with a chiral copper catalytic system, matching the advantages that chiral NHC ligands

2. The Selective Catalytic Formation of β-Boryl Aldehydes Through a Base-Free Approach; **A. Bonet**, V. Lillo, J. Ramírez, M. M. Díaz-Requejo, E. Fernandez.* *Organic and Biomolecular Chemistry*, **2009**, *7*, 1533.



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COMMUNICATION www.rsc.org/obc | Organic & Biomolecular Chemistry

The selective catalytic formation of β-boryl aldehydes through a base-free approach†

Amadeu Bonet,[a] Vanesa Lillo,[a] Jesús Ramírez,[a] M. Mar Díaz-Requejo[b] and Elena Fernández*[a]

Received 27th January 2009, Accepted 26th February 2009
First published as an Advance Article on the web 11th March 2009
DOI: 10.1039/b901767d

(NHC)Cu(I) complexes are key in a new strategy to selectively add a boron unit at the β-position of α,β-unsaturated aldehydes in the absence of a base.

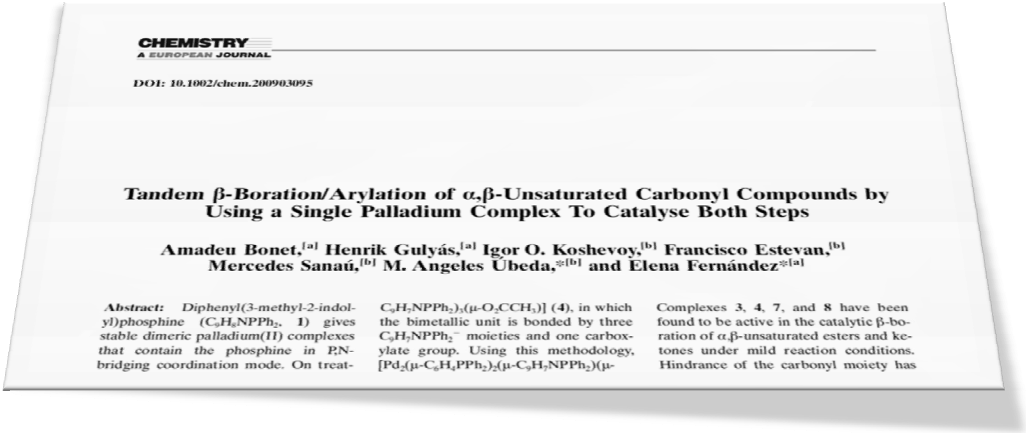
In the catalytic diboration of alkenes,[1] the metal-mediated 1,4-addition of diboron reagents to electron-deficient olefins is the most convenient approach for preparing β-boryl carbonyl compounds.[2] Of particular interest is the recent work on the asymmetric version of this reaction.[3] Conceptually, only one boryl unit from the diboron reagent is catalytically added to the β-position of the substrate, affording the 1,4-hydroborated product after a hydrolytic workup. The range of α,β-unsaturated carbonyl substrates that undergo 1,4-addition with

/pubs.rsc.org | doi:10.1039/B901767D

Table 1 (NHC)CuCl- and [(NHC)Cu(NCCH$_3$)]BF$_4$-catalysed β-boration of crotonaldehyde with B$_2$pin$_2$^{a}

Entry	Catalyst	Base	Conv. (%)^b	(%)^{b,c}
1	**1**	NaO^{t}Bu	99	52
2	**2**	NaO^{t}Bu	99	43
3	**3**	NaO^{t}Bu	99	60
4	**4**	NaO^{t}Bu	99	39
5	**5**	NaO^{t}Bu	99	48
6	**6**	NaO^{t}Bu	99	39
7	**3**	NaOMe	99	59
8	**3**	NaOAc	99	41

3. Tandem β-Boration/Arylation of α,β-Unsaturated Carbonyl Compounds by Using a Single Palladium Complex To Catalyse Both Steps; **A. Bonet**, H. Gulyás, I. O. Koshevoy, F. Estevan, M. Sanaú, M. A. Ubeda,* E. Fernández* *Chemistry: European Journal*, **2010**, *16*, 6382



CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903095

Tandem β-Boration/Arylation of α,β-Unsaturated Carbonyl Compounds by Using a Single Palladium Complex To Catalyse Both Steps

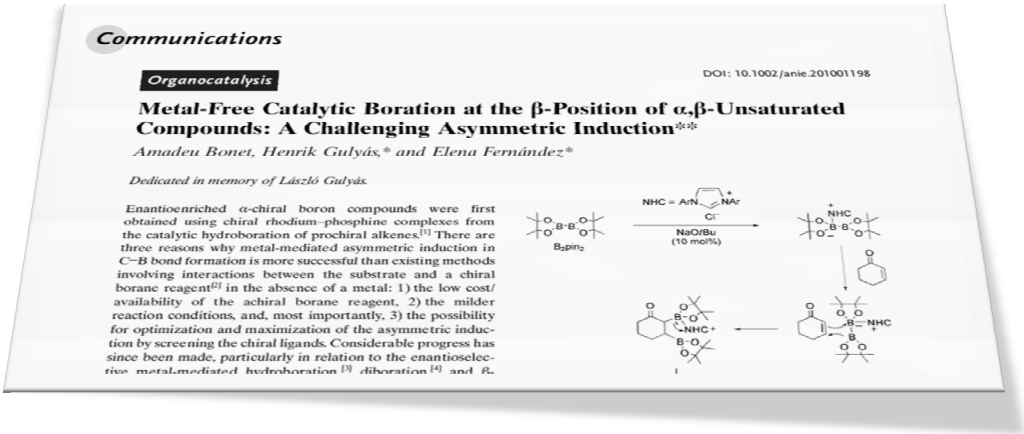
Amadeu Bonet,[a] Henrik Gulyás,[a] Igor O. Koshevoy,[b] Francisco Estevan,[b] Mercedes Sanaú,[b] M. Angeles Úbeda,*[b] and Elena Fernández*[a]

Abstract: *Diphenyl(3-methyl-2-indolyl)phosphine* (C$_9$H$_8$NPPh$_2$, **1**) *gives stable dimeric palladium(II) complexes that contain the phosphine in P,N-bridging coordination mode. On treat-*

C$_9$H$_7$NPPh$_2$)$_3$(μ-O$_2$CCH$_3$)] (**4**), in which the bimetallic unit is bonded by three C$_9$H$_7$NPPh$_2$$^-$ moieties and one carboxylate group. Using this methodology, [Pd$_2$(μ-C$_6$H$_4$PPh$_2$)$_2$(μ-C$_9$H$_7$NPPh$_2$)(μ-

Complexes **3**, **4**, **7**, and **8** have been found to be active in the catalytic β-boration of α,β-unsaturated esters and ketones under mild reaction conditions. Hindrance of the carbonyl moiety has

4. Metal-Free Catalytic Boration at the β-Position of α,β-Unsaturated Compounds: A Challenging Asymmetric Induction; **A. Bonet**, H. Gulyás,* and E. Fernández* *Angewantde. Chemie International Edition*, **2010**, *49*, 5130.



Communications

Organocatalysis

DOI: 10.1002/anie.201001198

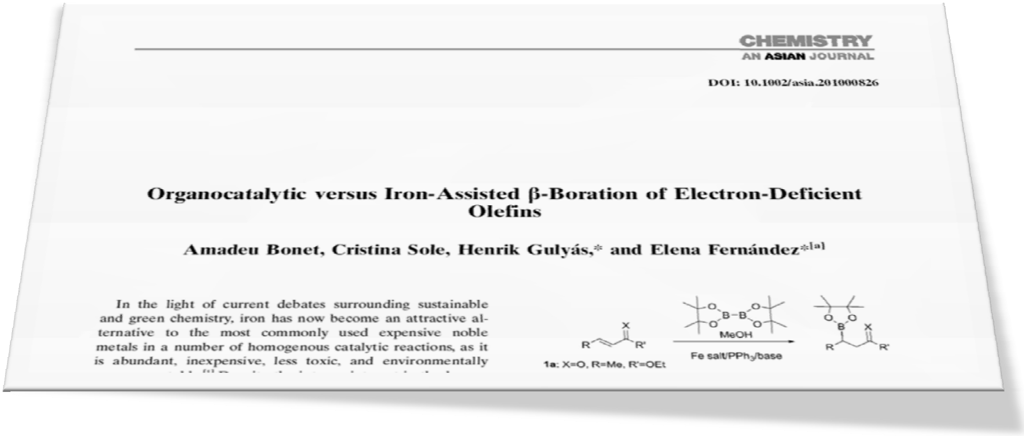
Metal-Free Catalytic Boration at the β-Position of α,β-Unsaturated Compounds: A Challenging Asymmetric Induction**

Amadeu Bonet, Henrik Gulyás, and Elena Fernández**

Dedicated in memory of László Gulyás.

Enantioenriched α-chiral boron compounds were first obtained using chiral rhodium–phosphine complexes from the catalytic hydroboration of prochiral alkenes.[1] There are three reasons why metal-mediated asymmetric induction in C−B bond formation is more successful than existing methods involving interactions between the substrate and a chiral borane reagent[2] in the absence of a metal: 1) the low cost/availability of the achiral borane reagent, 2) the milder reaction conditions, and, most importantly, 3) the possibility for optimization and maximization of the asymmetric induction by screening the chiral ligands. Considerable progress has since been made, particularly in relation to the enantioselective metal-mediated hydroboration,[3] diboration,[4] and β-

5. Organocatalytic versus iron assisted β-boration of electron deficient olefins *Chemistry: an Asian Journal*, **2011**, 6, 1011, **A. Bonet**, C. Sole, H. Gulyás* and E. Fernández*



CHEMISTRY
AN ASIAN JOURNAL

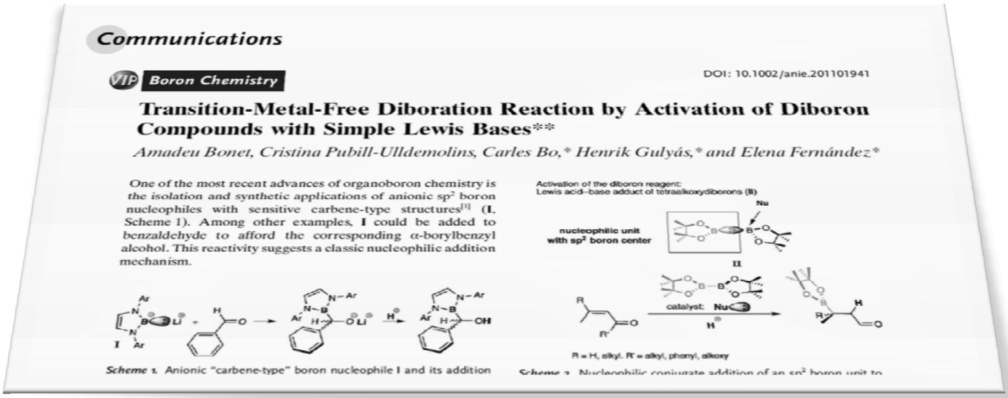
DOI: 10.1002/asia.201000826

Organocatalytic versus Iron-Assisted β-Boration of Electron-Deficient Olefins

Amadeu Bonet, Cristina Sole, Henrik Gulyás,* and Elena Fernández*[a]

In the light of current debates surrounding sustainable and green chemistry, iron has now become an attractive alternative to the most commonly used expensive noble metals in a number of homogenous catalytic reactions, as it is abundant, inexpensive, less toxic, and environmentally

6. Transition Metal-Free Diboration Reaction by Activation of Diborons with Simple Lewis-Bases; **A. Bonet**, C. Pubill-Ulldemolins, C. Bo*, H. Gulyás,* and E. Fernández* *Angewantde. Chemie International Edition*, **2011** *Angew. Chem. Int. Ed.* . **2010**, *49*, 5130 **(VIP)**



Communications

Boron Chemistry

DOI: 10.1002/anie.201101941

Transition-Metal-Free Diboration Reaction by Activation of Diboron Compounds with Simple Lewis Bases**

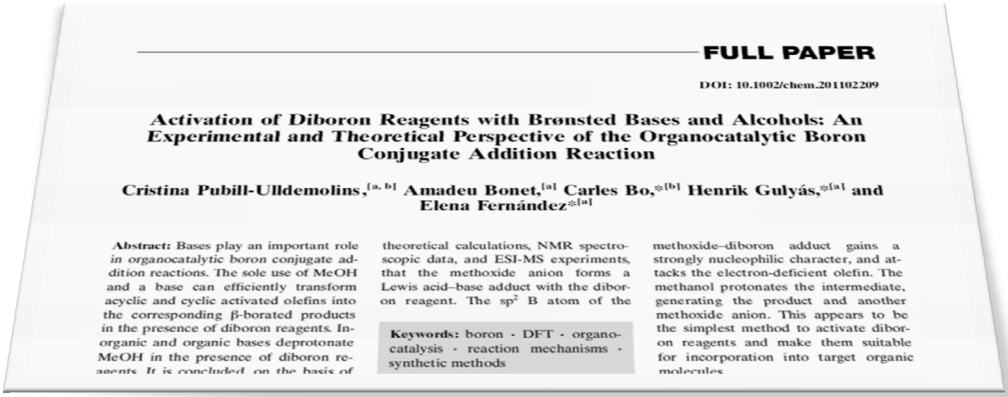
Amadeu Bonet, Cristina Pubill-Ulldemolins, Carles Bo, Henrik Gulyás,* and Elena Fernández**

One of the most recent advances of organoboron chemistry is the isolation and synthetic applications of anionic sp^2 boron nucleophiles with sensitive carbene-type structures[1] (**I**, Scheme 1). Among other examples, **I** could be added to benzaldehyde to afford the corresponding α-borylbenzyl alcohol. This reactivity suggests a classic nucleophilic addition mechanism.

Scheme 1. Anionic "carbene-type" boron nucleophile I and its addition

Scheme 2. Nucleophilic conjugate addition of an sp^2 boron unit to

7. Activation of Diboron Reagents with Brönsted Bases and Alcohols: An Experimental and Theoretical Prespective of the Organocatalytic Boron Conjugate Addition Reaction; C. Pubill-Ulldemolins, **A. Bonet**, C. Bo*, H. Gulyás,* and E. Fernández* *Chemistry: an European Journal,* **2011**, DOI: 10.1002/chem.201102209



FULL PAPER

DOI: 10.1002/chem.201102209

Activation of Diboron Reagents with Brønsted Bases and Alcohols: An Experimental and Theoretical Perspective of the Organocatalytic Boron Conjugate Addition Reaction

Cristina Pubill-Ulldemolins,[a, b] Amadeu Bonet,[a] Carles Bo,*[b] Henrik Gulyás,*[a] and Elena Fernández*[a]

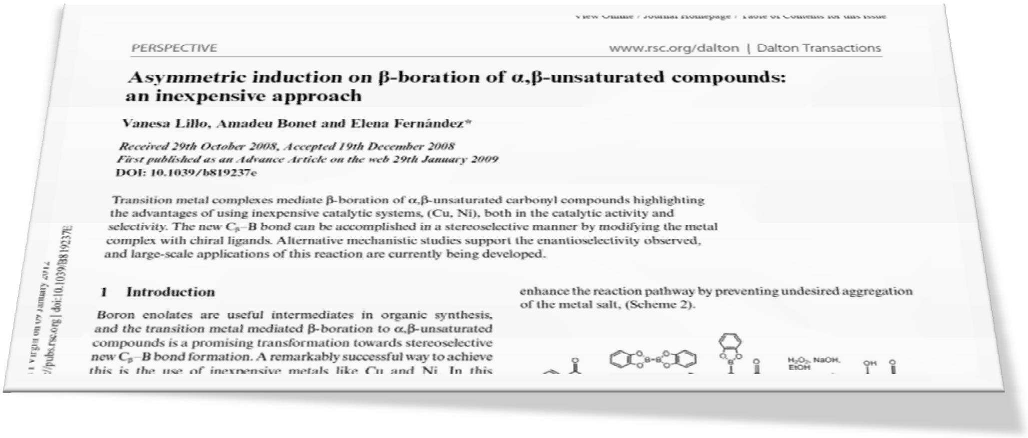
Abstract: Bases play an important role in organocatalytic boron conjugate addition reactions. The sole use of MeOH and a base can efficiently transform acyclic and cyclic activated olefins into the corresponding β-borated products in the presence of diboron reagents. Inorganic and organic bases deprotonate MeOH in the presence of diboron reagents. It is concluded, on the basis of theoretical calculations, NMR spectroscopic data, and ESI-MS experiments, that the methoxide anion forms a Lewis acid–base adduct with the diboron reagent. The sp^2 B atom of the methoxide–diboron adduct gains a strongly nucleophilic character, and attacks the electron-deficient olefin. The methanol protonates the intermediate, generating the product and another methoxide anion. This appears to be the simplest method to activate diboron reagents and make them suitable for incorporation into target organic molecules.

Keywords: boron · DFT · organocatalysis · reaction mechanisms · synthetic methods

8. Enantioselective Organocatalytic Diboration; **A.Bonet**, C. Pubill-Ulldemolins, C. Bo, H. Gulyás and E. Fernández (paper under preparation)

9.1.2 Prespectives and Reviews

9. Asymmetric Induction on β-Boration of α,β–Unsaturated Compounds: A Cheap Approach; V. Lillo, **A. Bonet**, E. Fernandez* *Dalton Transaction*, **2009**, 2899. (Perspective by invitation)



PERSPECTIVE

www.rsc.org/dalton | Dalton Transactions

Asymmetric induction on β-boration of α,β-unsaturated compounds: an inexpensive approach

Vanesa Lillo, Amadeu Bonet and Elena Fernández*

Received 29th October 2008, Accepted 19th December 2008
First published as an Advance Article on the web 29th January 2009
DOI: 10.1039/b819237e

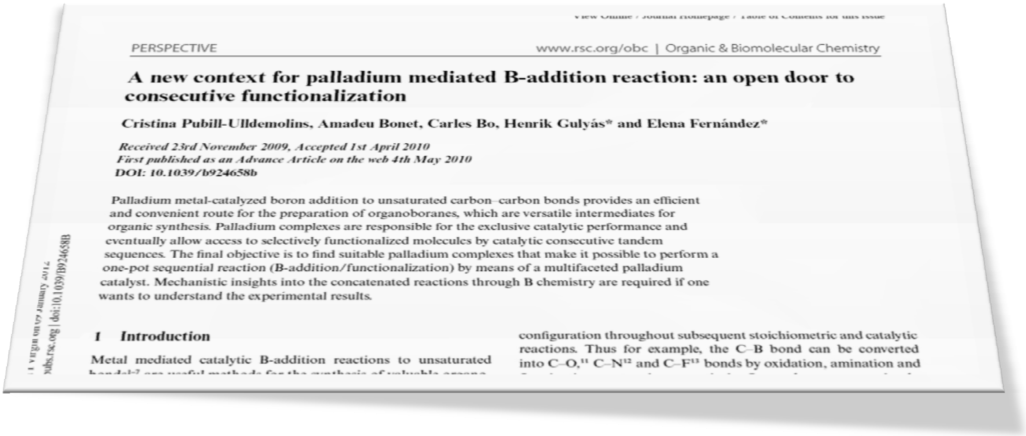
Transition metal complexes mediate β-boration of α,β-unsaturated carbonyl compounds highlighting the advantages of using inexpensive catalytic systems, (Cu, Ni), both in the catalytic activity and selectivity. The new C_β–B bond can be accomplished in a stereoselective manner by modifying the metal complex with chiral ligands. Alternative mechanistic studies support the enantioselectivity observed, and large-scale applications of this reaction are currently being developed.

1 Introduction

Boron enolates are useful intermediates in organic synthesis, and the transition metal mediated β-boration to α,β-unsaturated compounds is a promising transformation towards stereoselective new C_β–B bond formation. A remarkably successful way to achieve this is the use of inexpensive metals like Cu and Ni. In this

enhance the reaction pathway by preventing undesired aggregation of the metal salt, (Scheme 2).

10. A New Context for Palladium Mediated B-Addition Reaction: An Open Door to Consecutive Functionalization; C. Pubill-Ulldemolins, **A. Bonet**, C. Bo, H. Gulyás,* and E. Fernández* *Organic and Biomolecular Chemistry*, **2010**, *8*, 2667. (Perspective by invitation)



PERSPECTIVE www.rsc.org/obc | Organic & Biomolecular Chemistry

A new context for palladium mediated B-addition reaction: an open door to consecutive functionalization

Cristina Pubill-Ulldemolins, Amadeu Bonet, Carles Bo, Henrik Gulyás* and Elena Fernández*

Received 23rd November 2009, Accepted 1st April 2010
First published as an Advance Article on the web 4th May 2010
DOI: 10.1039/b924658b

Palladium metal-catalyzed boron addition to unsaturated carbon–carbon bonds provides an efficient and convenient route for the preparation of organoboranes, which are versatile intermediates for organic synthesis. Palladium complexes are responsible for the exclusive catalytic performance and eventually allow access to selectively functionalized molecules by catalytic consecutive tandem sequences. The final objective is to find suitable palladium complexes that make it possible to perform a one-pot sequential reaction (B-addition/functionalization) by means of a multifaceted palladium catalyst. Mechanistic insights into the concatenated reactions through B chemistry are required if one wants to understand the experimental results.

pubs.rsc.org | doi:10.1039/B924658B

1 Introduction

Metal mediated catalytic B-addition reactions to unsaturated

configuration throughout subsequent stoichiometric and catalytic reactions. Thus for example, the C–B bond can be converted into C–O,[11] C–N[12] and C–F[13] bonds by oxidation, amination and

11. Boron conjugate additions on electron deficient olefins towards selective 1,3-difunctionalization; **A. Bonet**, C. Solé, H. Gulyás,* and E. Fernández* *Current Organic Chemistry*, **2010**, *14*, 2531 (Review by invitation)

Current Organic Chemistry, 2010, 14, 0000-0000 1

Boron Conjugate Additions on Electron Deficient Olefins Towards Selective 1,3-Difunctionalization

Amadeu Bonet, Cristina Sole, Henrik Gulyás,* Elena Fernández*

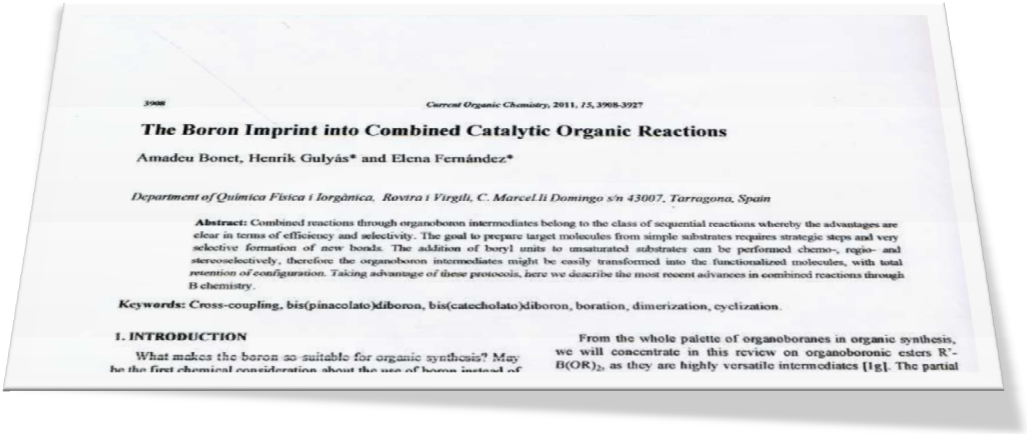
Dept Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcelli Domingo s/n, 43007 Tarragona, Spain

Abstract: The selective introduction of a boron unit in an organic framework opens new perspectives in both building block design and functionalization protocols.

The presence of carbonyl or imino groups in β position with regard to the boryl moiety makes them suitable organoboron intermediates for difunctionalized purposes. Catalytic synthetic methodologies have recently been developed to introduce a boryl group at the β-position of α,β-unsaturated esters, ketones, aldehydes, amides, nitriles, as well as imines and oximes. The asymmetric version favours the chiral C_β-B formation which can be eventually transformed into useful alcohols or acetyl functional groups. Alternatively, β-boronate carbonyl or imino compounds can be prepared via alkylation of an enolate with α-haloboronates esters. The subsequent route for the preparation of the chiral β-boronate derivatives required transesterification protocols that successfully provided a series of β-oximo boronates, *β-imino boronates and* β-carbonyl boronates, with chiral boryl units. This review will enable the reader to understand catalytic and *non-catalytic routes for the synthesis of* β-boronate carbonyl and imino compounds. The overall mechanistic insights and the perceptible influence of additives on these different synthetic processes, will be discussed. More emphasis will be placed on further applications of the β-boronate compounds in the synthesis of diols or aminoalcohols, in particular where β-chiral centres efficiently control further enantioselective transformation, despite their remote position.

SELECTIVE PREPARATION OF β-BORYL CARBONYL COMPOUNDS (BORON HOMOENOLATES)

12. The boron imprint on consecutive catalytic organic reactions; **A. Bonet**, H. Gulyás* and E. Fernández* *Current Organic Chemistry*, **2011**, *15*, 3908 (Special Issue)



3908 *Current Organic Chemistry*, 2011, *15*, 3908-3927

The Boron Imprint into Combined Catalytic Organic Reactions

Amadeu Bonet, Henrik Gulyás* and Elena Fernández*

Department of Química Física i Iorgànica, Rovira i Virgili, C. Marcel.li Domingo s/n 43007, Tarragona, Spain

Abstract: Combined reactions through organoboron intermediates belong to the class of sequential reactions whereby the advantages are clear in terms of efficiency and selectivity. The goal to prepare target molecules from simple substrates requires strategic steps and very selective formation of new bonds. The addition of boryl units to unsaturated substrates can be performed chemo-, regio- and stereoselectively, therefore the organoboron intermediates might be easily transformed into the functionalized molecules, with total retention of configuration. Taking advantage of these protocols, here we describe the most recent advances in combined reactions through B chemistry.

Keywords: Cross-coupling, bis(pinacolato)diboron, bis(catecholato)diboron, boration, dimerization, cyclization.

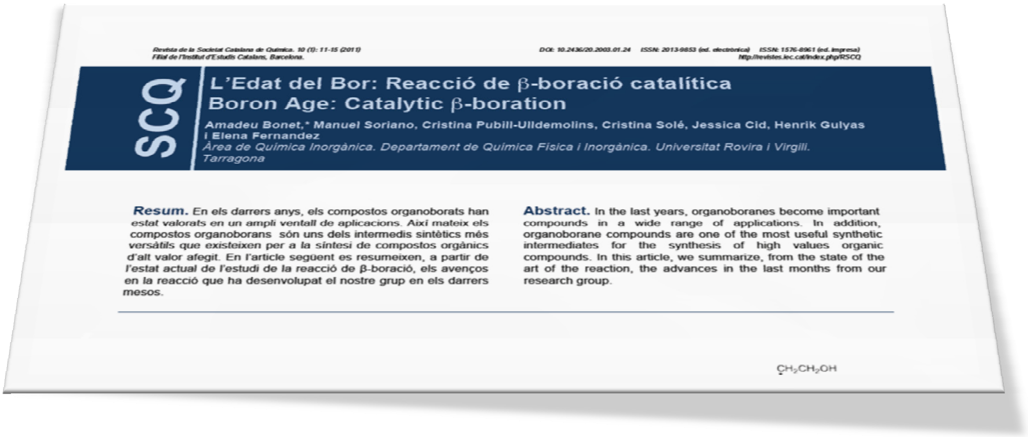
1. INTRODUCTION

What makes the boron so suitable for organic synthesis? May be the first chemical consideration about the use of boron instead of

From the whole palette of organoboranes in organic synthesis, we will concentrate in this review on organoboronic esters R'-$B(OR)_2$, as they are highly versatile intermediates [1g]. The partial

9.1.3 Not indexed journals, divulgation

13. L'Edat del Bor: Reacció de β-boració catalítica; The Boron Age: Catalytic β-boration; **A. Bonet**,* M. Soriano, C. Pubill-Ulldemolins, C. Solé, J. Cid, H. Gulyás and E. Fernández *Revista de la Societat Catalana de la Química; Catalan Chemical Society Journal*, **2011**, *10*, 11.



Revista de la Societat Catalana de Química, 10 (1): 11-15 (2011)
Filial de l'Institut d'Estudis Catalans, Barcelona.

DOI: 10.2436/20.2003.01.24 ISSN: 2013-9853 (ed. electrònica) ISSN: 1576-8961 (ed. impresa)
http://revistes.iec.cat/index.php/RSCQ

SCQ

L'Edat del Bor: Reacció de β-boració catalítica
Boron Age: Catalytic β-boration

Amadeu Bonet,* Manuel Soriano, Cristina Pubill-Ulldemolins, Cristina Solé, Jessica Cid, Henrik Gulyas i Elena Fernandez
Àrea de Química Inorgànica. Departament de Química Física i Inorgànica. Universitat Rovira i Virgili. Tarragona

Resum. En els darrers anys, els compostos organoborats han estat valorats en un ampli ventall de aplicacions. Així mateix els compostos organoborans són uns dels intermedis sintètics més versàtils que existeixen per a la síntesi de compostos orgànics d'alt valor afegit. En l'article següent es resumeixen, a partir de l'estat actual de l'estudi de la reacció de β-boració, els avenços en la reacció que ha desenvolupat el nostre grup en els darrers mesos.

Abstract. In the last years, organoboranes become important compounds in a wide range of applications. In addition, organoborane compounds are one of the most useful synthetic intermediates for the synthesis of high values organic compounds. In this article, we summarize, from the state of the art of the reaction, the advances in the last months from our research group.

CH_2CH_2OH

9.2 Prizes

2010 Best oral communication in Catalysis Symposium in the Sixth Meeting of Young Researchers of the Catalan Countries

2010 3th Best flash presentation – Euroboron 5

2011 Finalist of Young Boron Chemist Award in IMEBoron XIV

9.3 Posters and presentations

Conference: 16th International Symposium on Homogeneous Catalysis **Place:** Florence, Italy **Year:** 2008

Authors: <u>Amadeu Bonet</u>, Vanesa Lillo, Auxiliadora Prieto, Jesus Ramírez, M. Mar Díaz-Requejo, P. J. Perez, Elena Fernández **Title:** *Cu-NHC mediates selective catalytic approach to β-boryl compounds* **Contribution:** Poster

Conference: XIII IMEBoron **Place:** Platja d'Aro, Spain **Year:**2008

Authors: <u>Amadeu Bonet</u>, Vanesa Lillo, Auxiliadora Prieto, Jesus Ramírez, M. Mar Díaz-Requejo, P. J. Perez, Elena Fernández **Title:** *Cu-NHC mediates selective catalytic approach to β-boryl compounds* **Contribution:** Poster

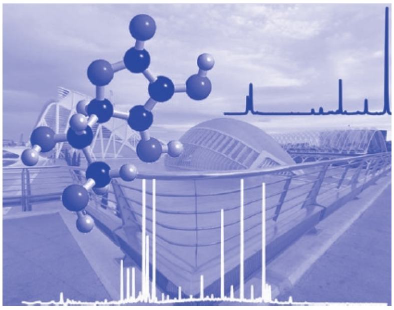
Conference: Renacom 2009, International Symposium on Organometallic Chemistry and Catalysis **Place:** Tetuan, Marroco **Year:** 2009

Authors: <u>Amadeu Bonet</u>, Vanesa Lillo, Auxiliadora Prieto, Jesus Ramírez, M. Mar Díaz-Requejo, P. J. Perez, Elena Fernández **Title:** *Cu-NHC mediates selective catalytic approach to β–boryl compounds* **Contribution:** Poster

Conference: ISHHC XIV Symposium on Relations between Homogeneous and Heterogeneous Catalysis (ISHHC XIV) **Place:** Stockholm, Sweden **Year:** 2009.

ISHHC XIV Stockholm
13-18 September 2009

Authors: Amadeu Bonet, Mª Angeles Ubeda, Elena Fernández **Title:** *Functionalization of α,β-unsaturated carbonyl compounds via Pd-mediated tandem β-boration / cross-coupling reactions* **Contribution:** Poster



Conference: Sixth Meeting of Young Researchers of the Catalonian Countries **Place:** Valencia, Spain **Year:** 2010

Authors: Amadeu Bonet, M Soriano, C. Pubill, C. Sole, J. Cid, H. Gulyás, E Fernandez **Title:** *Addicions catalitiques conjugades de bor cap a la formacio selectiva de β-boril carbonils i imines; Catalytic conjugated boron addition to the selective formation of b-boryl carbonyl and imine compounds* **Contribution:** Oral communication: A. Bonet

Conference: Euroboron 5 **Place:** Edinburgh, Scotland **Year:**2010

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Authors: A. Bonet, H. Gulyás, E. Fernánez **Title:** *Enantioselective β-boration*. **Contribution:** Poster-flash

Conference: GEQO **Place:** Huelva, Spain **Year:** 2010

Authors: A. Bonet, H. Gulyás, E. Fernández **Title:** *β–boración de compuestos α,β–insaturados con hierro; Catalytic β-boration of α,β-unsaturated compounds with Iron* **Contribution:** Poster

Conference: XXXIII Reunión Bienal de la RSEQ **Place:** Valencia, Spain **Year:** 2011

Authors: A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández **Title:** *Organocatalytic diboration of unactivated olefins: Enantioselective Approach* **Contribution:** Poster-flash

Conference: IME Boron XIV **Place:** Toronto, Canada **Year:** 2011

Authors: A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández **Title:** *Organocatalytic diboration of unactivated olefins: Enantioselective Approach* **Contribution:** Invited Lecture

Cu-NHC mediates selective catalytic approach to β-boryl compounds

Amadeu Bonet,[a] Vanesa Lillo,[a] Auxiliadora Prieto,[b] M. Mar Díaz- Requejo,[b]
Jesús Ramírez,[a] Pedro J. Pérez,[b] Elena Fernández[a]

[a]Dpt. Química Física i Inorgànica, Universitat Rovira i Virgili, Marcel.lí Domingo s/n,43007 Tarragona, (Spain)
[b]Departamento de Ingeniería Química, Química Física y Química Orgánica. Universidad de Huelva, 21007-Huelva, (Spain)
[c]Laboratorio de Catálisis Homogénea, Dpt de Química y Ciencia de los Materiales, Universidad de Huelva, 21007-Huelva (Spain)

OBJECTIVE

The asymmetric induction on the β-boration of α,β-unsaturated carbonyl compounds with bis(pinacolato)diboron through chiral carbene N-heterocyclic ligands modifying Cu salts

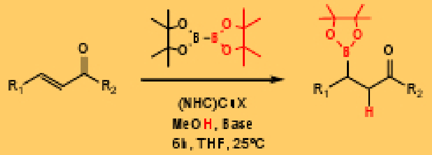
PERSPECTIVE

In the course of the development of catalytic diboration of alkenes, the metal-mediated 1,4-addition reaction of diboron reagents to electron deficient olefins rankes as the most convenient approach for the preparation of β-boryl carbonyl compounds,[1] highlighting the recent approaches towards the asymmetric version.[2]

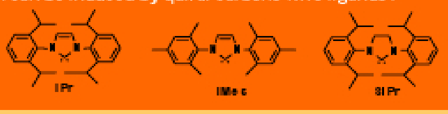
Can Cu(I) modified with carbene NHC ligand perform the reaction?

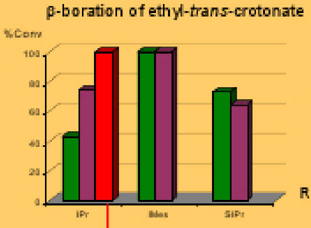
How important is the base?

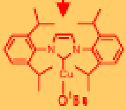
Asymmetric induction can be induced by quiral carbene NHC ligands?



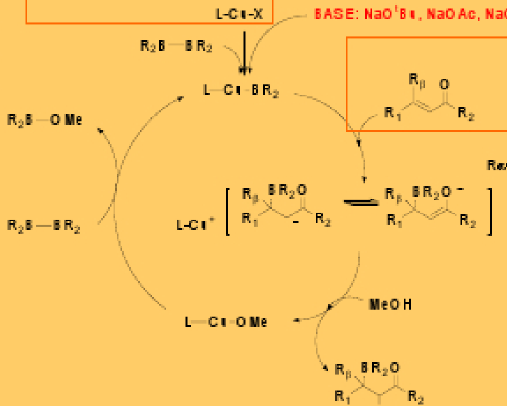
NHC ligands:



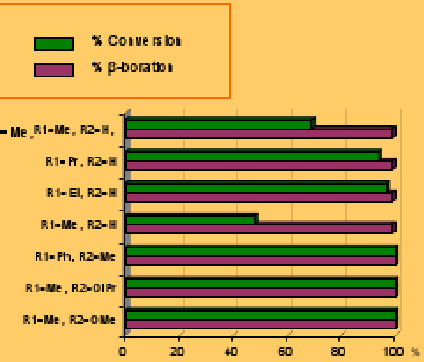




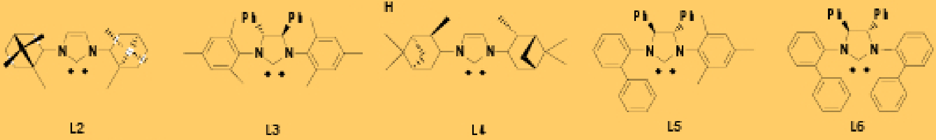
The base free approach

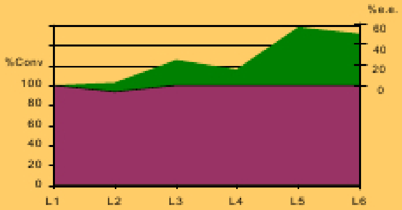


The favored 1,4- versus 1,2-diboration on aldehydes

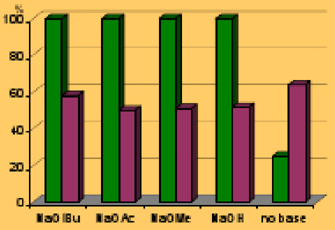


Asymmetric induction

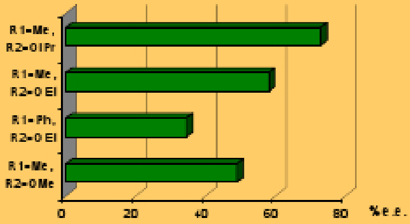




Asymmetric β-boration of ethyl-*trans*-crotonate



The basic influence on the asymmetric β-boration of ethyl-*trans*-crotonate with L_5CuCl



CONCLUSIONS

Cu(I) salts modified with IPr, IMes, SIPr carbene NHC ligands conduct successfully the β-boration of α,β-insaturated esters, ketones and aldehydes, being the 1,4 addition favored versus the 1,2 addition.

The base can be avoided when LCuOR precatalyst is used instead.

Up to 73% of e.e. can be obtained with Cu-carbene NHC ligands with quirality on the backbone of the N-heterocycle

1. T. B. Marder, *Organomet. Chem.* 2008, 34, 46;
2. S. Mun, J.-E Lee, J. Yun, *Org. Lett.*, 2006, 8, 4887; J.-E Lee, J. Yun, *Angew. Chem. Int. Ed.*, 2007, 47, 145.

Functionalization of α,β-unsaturated carbonyl compounds via Pd-mediated tandem β-boration / cross-coupling reactions

Amadeu Bonet, Mª Anegles Ubeda and Elena Fernandez*

Department of Inorganic Chemistry. Universitat de València. Doctor Moliner 50, 46100 Burjassot, València (Spain)
Department of Physical and Inorganic Chemistry, Universitat Rovira i Virgili, Marcel.lí Domingo s/n, 43007 Tarragona, (Spain)

OBJECTIVE

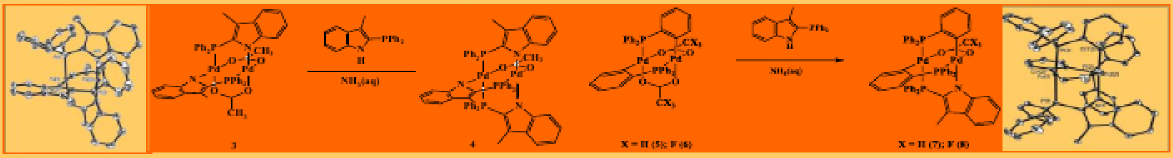
Design and synthesis of Pd-complexes which are active catalysts for both boration and cross coupling reactions.

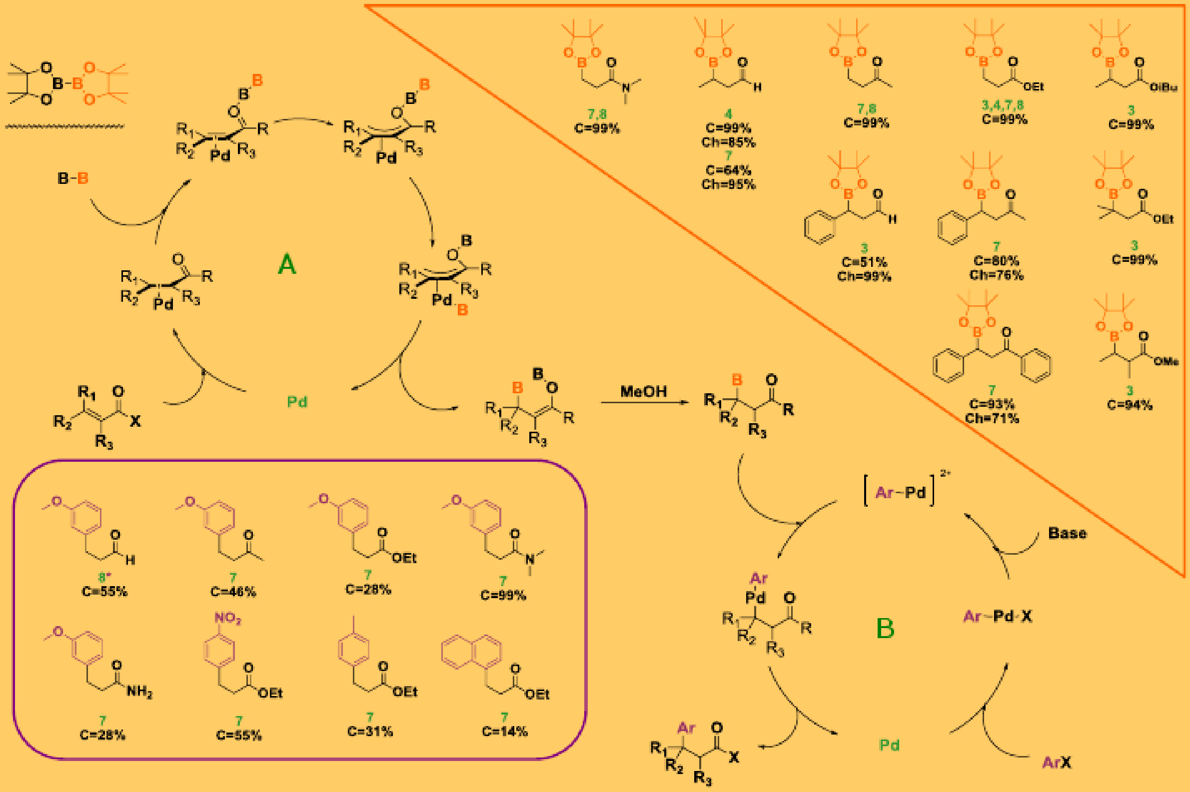
Selective β-arylation of various α,β-unsaturated carbonyl compounds by tandem boration-Suzuki coupling reactions.

Keywords: catalysis, palladium, dinuclear complexes, β-boration, Suzuki coupling, tandem reactions

PERSPECTIVE

Electronic directing effects has revealed a trend in regioisomeric organoboronate formation in the metal mediated β-boration reaction of α,β-unsaturated carbonyl substrates¹ (Cycle A). Despite the selective control of C-B formation and the retention of configuration in the functionalisation process from organoborane intermediates to target products, to the best of our knowledge the oxidation-acylation reaction is the only functionalisation protocol that has been explored so far.²





A: Standard conditions: Substrate / Pd = 1/0.05. B_2pin_2 = 1.5 eq., Cs_2CO_3 = 1.5 eq. H_2O = 1.5 eq., MeOH =10eq. Solvent: Toluene (2mL).T = 25ºC, 6h.
A+B: Standard conditions: Substrate / Pd = 1/0.05. B_2pin_2 = 1.5 eq., Cs_2CO_3 = 1.5 eq. H_2O = 1.5 eq., MeOH =10eq. Solvent: THF (2mL).T = 25ºC, 6h. Addition Cs_2CO_3 = 3eq., Aryl Bromide = 2eq. , Solvent/H_2O(1 / 0.1). T = 70ºC.24h. *Solvent = Toluene

1. (a) Marder, T. B. *J. Organomet. Chem.* **2008**, *34*, 46. (b) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics*, **2008**, *27*,4443. (c) Lillo, V.; Bonet, A.; Fernandez, E. *Dalton Transaction*, **2009**, 2899.
2. (a) Lee, J.-E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145. (b) Sim, H.-S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939. (c) Chea, H.; Sim, H.-S.; Yun, J. *Adv.Synth. Catal.*, **2009**, *351*, 855.(d) Lillo, V. Prieto, A, Bonet, A, Diaz Requejo, M. M.; Ramírez, J.; Fernandez, E. *Organometallics*, **2009**, *28*, 659.(e) Fleming, W. J.; Muller-Bunz, H.; Lillo, V.; Fernandez, E., Guiry, P. J. *Org. Biomol. Chem.*, **2009**, *7*, 2520. (f) Lillo V.; Geier, M. J.; Wetscott, S. A.; Fernandez, E. *Org. Biomol. Chem.*, **2009**, DOI 10.1039 / B 909341A

CONCLUSIONS

New dinuclear paladium(II) complexes containing the diphenyl(3-methyl-2-indolyl)phosphine as P,N-bridging coordination ligand, successfully catalyzed both the selective β-boration of various α,β-unsaturated carbonyl compounds and the subsequent Suzuki couplings with functionalized arylhalide reagents. The two reactions have been carried out „one pot", without the isolation of the of the boronic ester intermediates. Stereoselective versions of these new tandem reactions are under investigation.

Enantioselective β-boration

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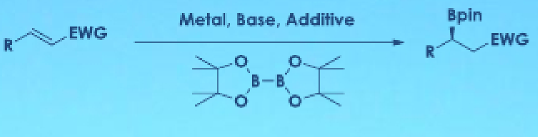
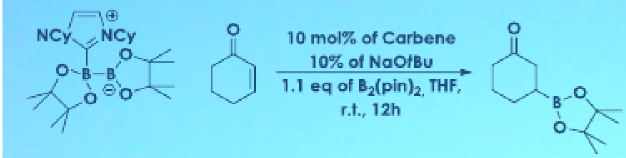
amadeu.bonet@urv.cat

• PRESPECTIVE...

α-Chiral C-B bonds are important synthons for the stereoselective synthesis of new functionalization bonds. Enantioselective β-boration of electron deficient olefins has been highlighted in the last years[1]. It's the only reaction that we can obtain selectively α,γ-carbonyl boranes compounds.

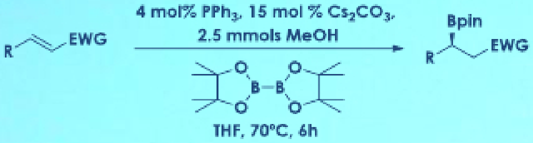




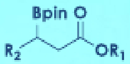
Last year, Hoveyda et all, described a new methodology based on the activation of the B_2pin_2 by N-heterocyclic carbenes (NHC)[2]. This was the first example of metal-free β-borylation. Under these conditions, the the use of phosphines to activate the diboron is not possible.

• RESULTS...

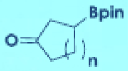
We develop a new methodology that use phosphines to activate the bis(pinacolato)diboron[3].



R_1=Methyl	R_2= Propyl	Conv= 91%
R_1=Methyl	R_2= Pentyl	Conv=90%
R_1=Ethyl	R_2= Methyl	Conv=99%
R_1=Phenyl	R_2= Methyl	Conv=99%

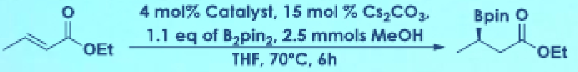


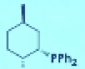
R_1=Methyl	R_2= Methyl	Conv= 99%
R_1=Ethyl	R_2= Methyl	Conv=99%
R_1= Iso-propyl	R_2= Methyl	Conv=51%
R_1= Tert-Butyl	R_2= Methyl	Conv=54% (16h)

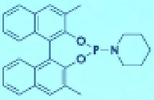


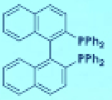
n=0 Conv=99% (16h)
n=1 Conv=99% (16h)

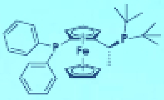
- The availability of chiral phosphines opens a new range of possibilities to induce enantioselectivity

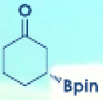


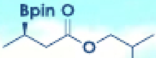

Conv=74%
Ee=<5%


Conv=54%
Ee=35%


Conv=99%
Ee=77%


Conv=94%
Ee=88%


(R)-(S)-Josiphos:
Conv:62% Ee:36%

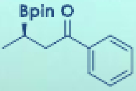

(R)-BINAP:
Conv:53% Ee:66%


(R)-(S)-Josiphos:
Conv:61% Ee:82%


(R)-(S)-Josiphos:
Conv:99% Ee:83%


(R)-(S)-Josiphos:
Conv:79% Ee:80%


(R)-(S)-Josiphos:
Conv:89% Ee:95%


(R)-(S)-Josiphos:
Conv:62% Ee:36%

1) Schiffner, J. A., Müther, K., Oestreich M. *Angew. Chem. Int. Ed.* **2010**, 49, 2–5 2) Lee, K., Zhugarlin, A., Hoveyda, A., *JACS*. **2009**, 131, 7253, 3) Bonet, A. Gulyás, H, Fernándnez, E. *Angew. Chem. Int. Ed.* . **2010**, 49, 5130

β-BORATION OF α,β-UNSATURATE COMPOUNDS WITH IRON(MAN)

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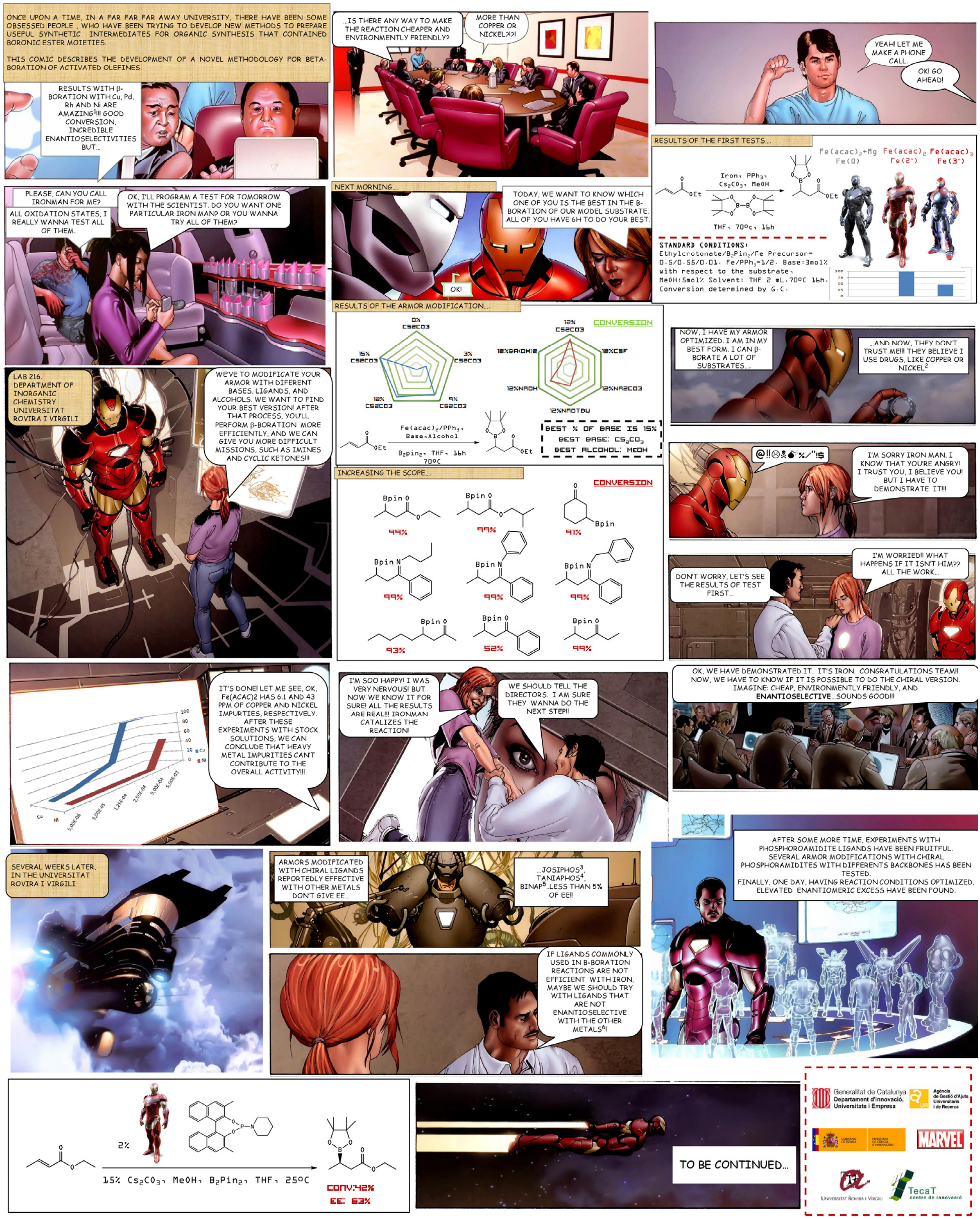

Generalitat de Catalunya Departament d'Innovació, Universitats i Empresa
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UNIVERSITAT ROVIRA I VIRGILI
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1) J. A. SCHIFFNER, K. MTHER, M. OESTREICH; ANGEW INT ED **2010**, *49*, 2 2) S. L. BUCHWALD, C. BOLM, ANGEW. CHEM. INT. ED. **2009**, *48*, 5586 3) J.-E. LEE, J. YUN, ANGEW. CHEM. **2008**, *120*, 151 4) V. LILLO, M. J. GEIER, S. A. WESTCOTT, E. FERNNDEZ, ORG. BIOMOL. CHEM. **2009**, 7, 4674 5) A. BONET, H. GUYLAS, E. FERNANDEZ ANGEW. CHEM. INT. ED. **2010**, *49*, 5130 6) H.-S. SIM, X. FENG, J. YUN, CHEM. EUR. J. **2009**, *15*, 1939

Organocatalytic diboration of non-activated olefins; enantioselective approach

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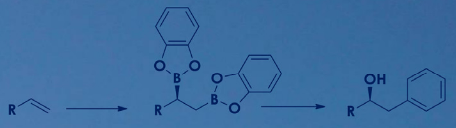
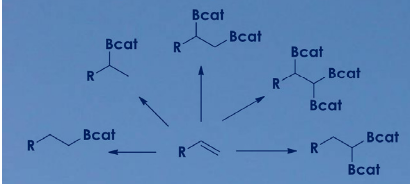
PRESPECTIVE…

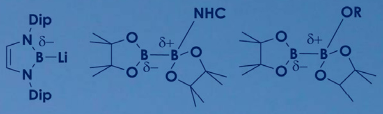
Diboron compounds are probably one of the most versatile intermediates for organic synthesis: both C-B linkages can be easily and independently transformed into C-O, C-N and C-C bonds[1]





Up to date, the only method to add tetralkoxydiborons to non-activated alkenes has been known to be the application of transition metal complexes as catalysts. These catalytic systems are usually expensive, and their chemoselectivity is also often unsatisfactory[2].

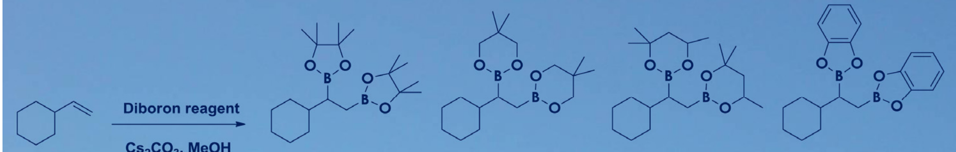
One of the recent advances in the boron chemistry is the synthesis of boryl units with nucleophilic character. Our approach is based on a very convenient activation of diboron reagents with simple Lewis bases. These nucleophilic Lewis acid-base adduct have been successfully used in assymmetric β-boration of α,β-unsaturated carbonyl compounds.[3]



Nozaki Hoveyda Fernández

GOAL AND RESULTS

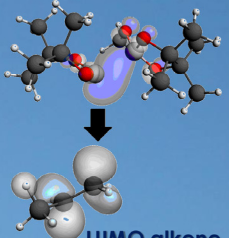
To extend the methodology to other substrates: non activated olefins:[4]



Conversion: 92%	Conversion: 73%	Conversion: 60%	Conversion: 85%
Chemoselectivity: 97%	Chemoselectivity: 99%	Chemoselectivity: 99%	Chemoselectivity: 99%
GC Yield: 87%	GC Yield: 72%	GC Yield: 59%	GC Yield: 84%
Isolated Yield: 71%	Isolated Yield: 59%	Isolated Yield: 56%	Isolated Yield of diol: 82%

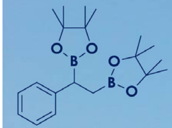
Mechanistic insights:

HOMO $B_2pin_2 \cdot MeO^-$

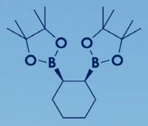


LUMO alkene

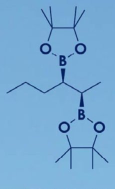
Substrate scope



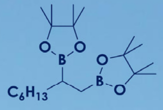
Conv: 82% Chem: 99%
Isolate Yield: 74%



Conv: 84% Chem: 99%
Isolate Yield: 65%

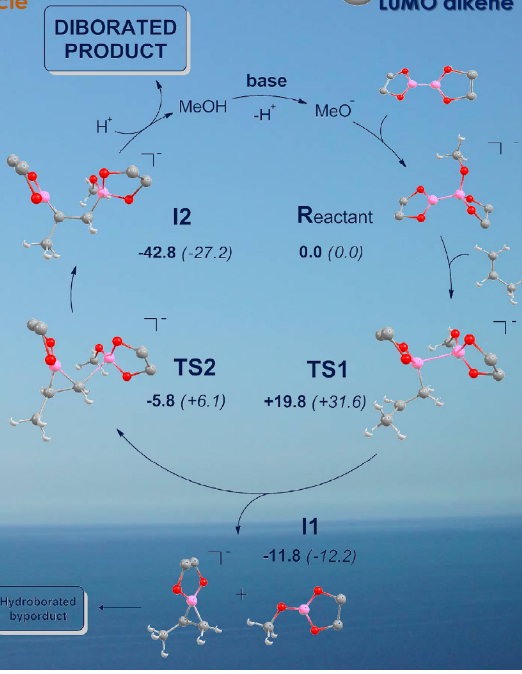


Conv: 92% Chem: 93%
[*Syn*/*Anti* 95:5]
Isolate Yield: 69%

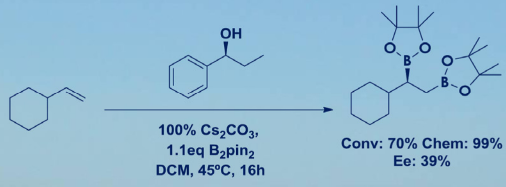


Conv: 98% Chem: 99%
Isoalte Yield: 71%

Catalytic cycle



Enantioselective approach



Conv: 70% Chem: 99%
Ee: 39%

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4) **A. Bonet, H. Gulys, E. Fernndez**, *Angew. Chem*. **2010**, *122*, 5256;. *Angew. Chem. Int. Ed.* . **2010**, *49*, 5130