SYNTHESIS OF AMINO ALCOHOLS THROUGH ONE-POPT CATALYTIC BORON ADDITION SEQUENCES

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Synthesis of amino alcohols through one-pot catalytic boron addition sequences

DOCTORAL THESIS

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Departament de Química Física I Inorgànica

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Dra. Maria Elena Fernández, professora titular del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili,

FAIG CONSTAR:

Que el present treball, titulat **"Synthesis of amino alcohol through one-pot catalytic boron addition sequences"**, que presenta la Sra. Cristina Solé Marcé per a l'obtenció del títol de Doctor en Química, ha estat realitzat sota la meva direcció i la co-direcció del Dr. Henrik Gulyás, del Departament de Química Física i Inorgànica de la Univesitat Rovira i Virgili, i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, 24 de maig del 2013

Dra. Maria Elena Fernández

Dr. Henrik Gulyás

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Quatre anys...són molts dies, molts minuts, molts segons per compartir moltes experiències, molts bons moments, molts "no tant" bons moments amb molta gent…Així que…fer els agraïments ja no d'una tesis…sinó d'una època de la meva vida…és extremadament difícil! I la dificultat no recau en expressar la meva gratitud, sinó TOT el contrari! Tinc TANTES coses que agrair…a TANTA gent que nombrar…que no sé com fer-ho. Així que he decidit, ser força selectiva i agrair els moments, detalls, fets que m'han marcat i que recordaré per tota la meva vida, ja sigui la vida científica com en la vida personal. Per això, d'anta mà, vull disculpar-me si algú no es sent reflectit en aquest escrit. D'altra banda, els que hi apareixeu, que sapigueu que no és una simple cortesia…sinó que hi esteu perquè heu SIGNIFICAT quelcom per mi!

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quan estàs lluny…es molt més senzill! Per això moltes gràcies avis! Per molt que no entengueu gaire "això de la investigació", veieu que és important per mi i respecteu les meves decisions encara que impliquin la vostra preocupació i us hagin deixat alguna nit sense poder dormir…No sé com dir-vos lo molt que us estimo! I com no…els que més em recolzen en les meves "lokures" són els meus pares! MOLTES GRÀCIES Paparruchi i Mamita!!! Sou els que m'ajudeu a aixecar-me…sou els que m'obriu la finestra quan no puc respirar…sou els que m'abraceu quan simplement necessito una abraçada…Ho sou TOT per mi! Sense vosaltres…jo NO seria RES!

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castells, de política, d'educació i de…altres coses que no nombraré! ☺! A cadascun de vosaltres us aprecio d'una manera singular i, per això, us recordaré:

La **Laia** → Per la teva senzillesa, mai crides l'atenció, sembla que no hi siguis però hi ets i això és lo més important! ☺!

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El **ChemistCasteller** (Marc) → Aquest noi ho té TOT! És intel·ligent, pencaire i divertit! I a més a més catalanista i casteller, que més es pot demanar?¿ Ah si…un Ferrari! Llàstima que fumi…! ☺!

El **Gerard** → És el noi "metrosexual" del laboratori, és un exemple de la nova generació "d'homes" d'aquesta societat…però és molt bon noi i estic segura que al final farà un excel·lent treball dins el món bor-fluor! ☺!

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de dir, però…amb molta autocrítica i ganes d'aprendre, coses d'admirar! Gràcies pels teus consells sobre cycling, converses que seran difícils d'oblidar! ☺!

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recordar el perquè de les coses...em feu recordar qui sóc...em feu recordar la meva il·lusió...els meus objectius! Simplement...GRÀCIES per estar aquí...per formar part de mi...per formar part de la meva VIDA!

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"CrisUtena&Friends"

"L'únic obstacle ets tu mateix, no tinguis por…amb constància i esforç ho aconseguiràs tot!"

Esteve Solé Boix (el meu pare)

"Sense il·lusió no ets res…no la perdis mai!"

Maria Marcé Florensa (la meva mare)

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1. Interest of amino alcohols

The general chemical structure of amino alcohols is characterized by containing both an amino and an alcohol functional group, and thus provides the combination of the physical features and chemical reactivity of both components. Medical Subject Heading (MeSH) [1] identifies six relevant type of amino alcohols according to their medical applications (Figure 1.1).

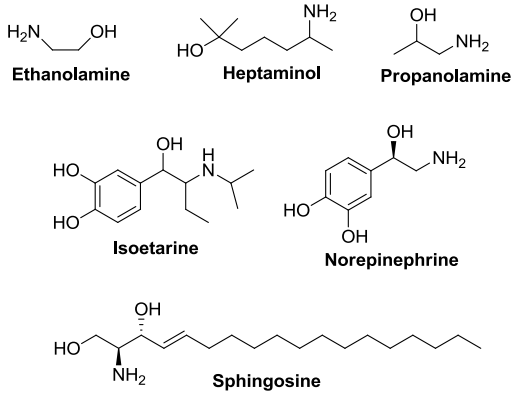


Figure 1.1 Classification of amino alcohol drugs for Medical Subject Heading (MeSH)

However, in classical organic chemistry the amino alcohols can be classified according to the relative position of the two functional groups as α, β or γ–amino alcohols (Figure 1.2). [2]

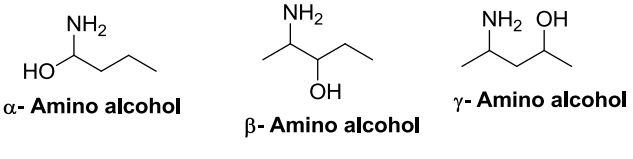


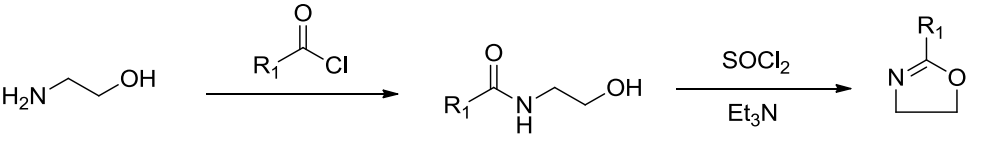
Figure 1.2 Structures of the most common type of amino alcohol.

The α-amino alcohols are less common due to the instability of the alcohol and the amine group located at the same carbon.

In contrast, the β– or γ– amino alcohols are important building blocks which have been extensively studied due to their applications. The most remarkable applications can be divided into three different topics:

a) Synthesis of materials:

The double functionality of amino alcohols makes them useful as raw materials in polymer synthesis. One of the best known reactivity involves the interaction with carboxylic acids to form the oxazoline structure (Scheme 1.1). [3]



Scheme 1.1 Synthesis of 2-oxazoline rings from carboxylic acids using thionyl chloride.

Moreover, 2-oxazolines can undergo cationic ring-opening polymerization to form poly(2-oxazoline)s. [4] These are polyamides and can be regarded as analogues of peptides and they have numerous potential applications as biomaterials (Figure 1.3). [5]

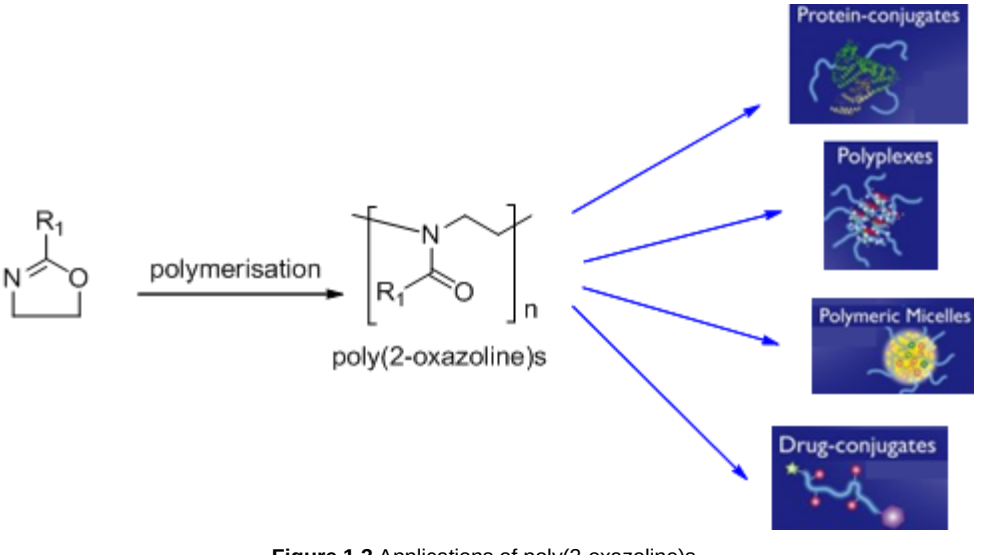


Figure 1.3 Applications of poly(2-oxazoline)s.

The use of amino alcohols in coatings is not limited to the synthesis of polymers. Indeed, most of the amino alcohols utilized by manufacturers of coatings are used for the dispersion of pigments in water-based paints or as an amine neutralizer to solubilize acid-functional polymers in water (Figure 1.4). [6]

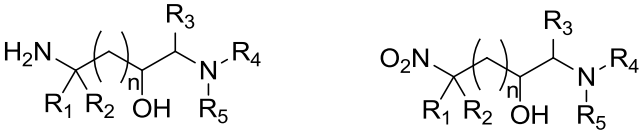


Figure 1.4 Amino alcohol compounds that are useful as neutralizing agents for aqueous based paints and coatings.

The isopropanolamines are common chemicals that can be used as emulsifiying agents. [7] They appear in personal care products such as cosmetics and creams, in home maintenance products such as floor polishes and cleaners, and in industrial products such as insecticide sprays and asphalt emulsions (Figure 1.5).

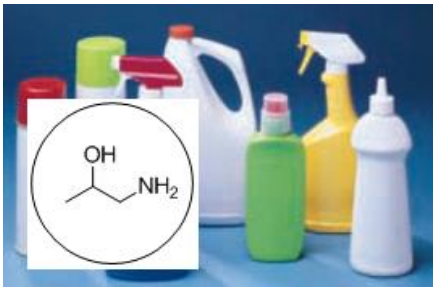


Figure 1.5 Cleaning products are made from derivatives of isopropanolamines

AMP-95 is an alkanolamine which can be used very efficiently in metalworking-fluid and boiler water treatment. [8] It provides excellent corrosion inhibition for metals of construction, efficient absorption of CO_2 and emulsion and thermal stability (Figure 1.6).

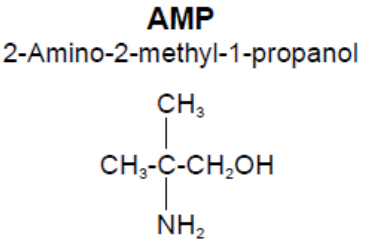
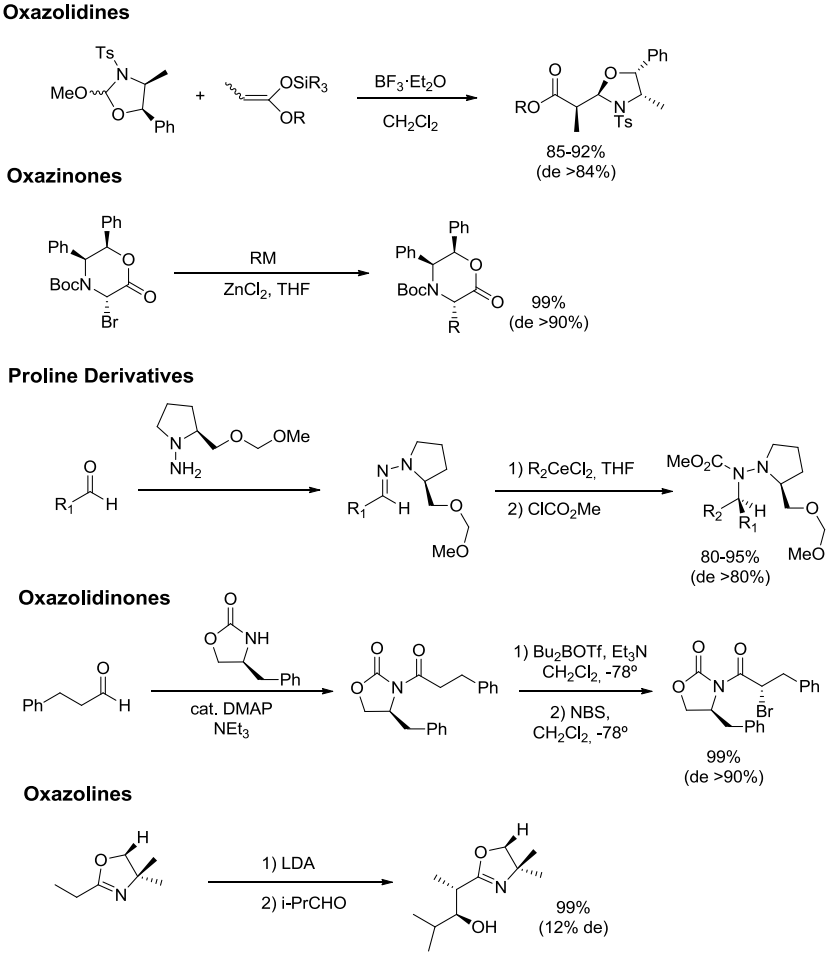


Figure 1.6 AMP-95, 2-Amino-2-methyl-1-propanol, is a primary amino alcohols made by ANGUS Chemical Company.

b) Asymmetric organic synthesis:

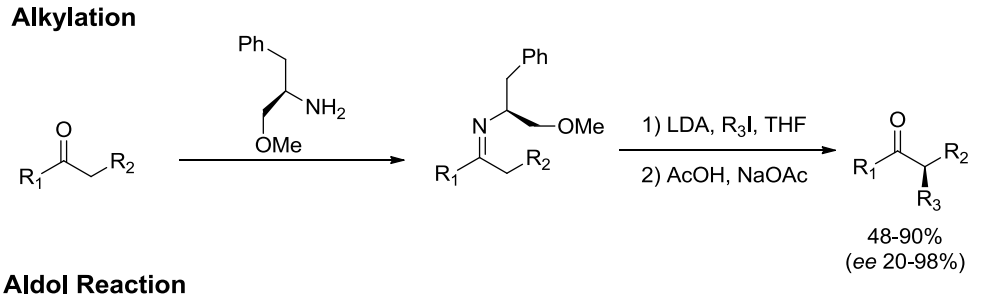
Chiral amino alcohols have extensively been used in asymmetric synthesis as auxiliaries or ligands due to their structure and chemical properties. The two heteroatoms can be bound to a Lewis acid, transition metal or achiral starting material and, moreover, they allow great flexibility and they are also useful as source of chiral centers. They are more robust, easier to synthesize and less chemically sensitive than chiral phosphorus compounds which provide distinct advantages to their application in asymmetric organic synthesis. [9]

The chiral information can be efficiently transferred to organic substrates in synthetic routes, in particular these five membered ring derivatives, such as: oxazolidines, [10] oxazinones, [11] proline derivatives, [12] oxazolidinones, [13] and oxazolines (Scheme 1.2). [14]



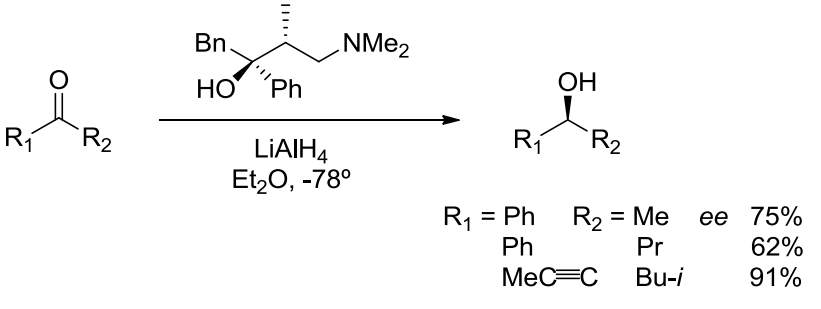
Scheme 1.2 Applications of chiral amino alcohols in organic synthesis.

Alternatively, the acyclic β–amino alcohols have been used in alkylations [15] or aldol reactions [16] as chiral auxiliaries (Scheme 1.3).



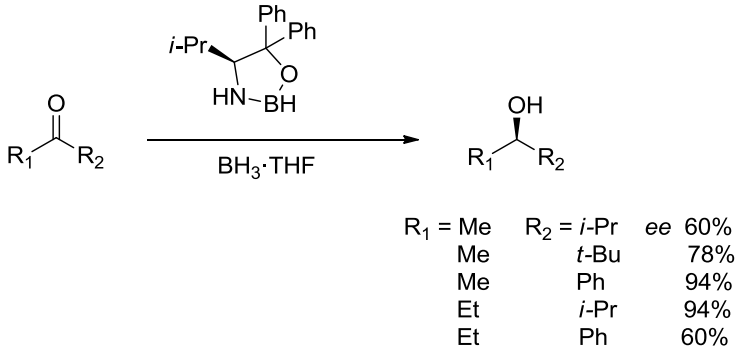
Scheme 1.3 Some examples where acyclic β–amino alcohols are used as chiral auxiliaries.

Amino alcohols have also been used to modify lithium aluminum hydride, and when used in the reduction of aryl alkyl ketones and propargylic ketones they provide high enantioselectivities [17] (Scheme 1.4).



Scheme 1.4 β-Amino alcohols used as chiral ligands in reduction of C=O towards enantioenriched alcohols.

Other application is the use of β–amino alcohols as chiral ligands for borohydride reductions of ketones (Scheme 1.5). [18]



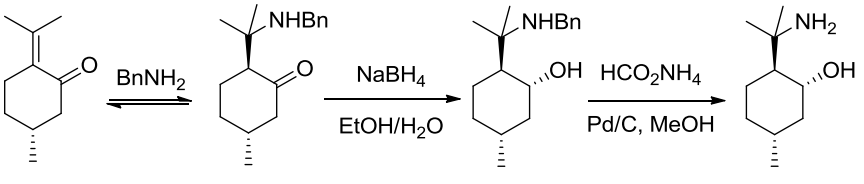
R_1 = Me	R_2 = *i*-Pr	*ee*	60%
Me	*t*-Bu		78%
Me	Ph		94%
Et	*i*-Pr		94%
Et	Ph		60%

Scheme 1.5 The use of β-amino alcohols as chiral ligands for borohydride reductions.

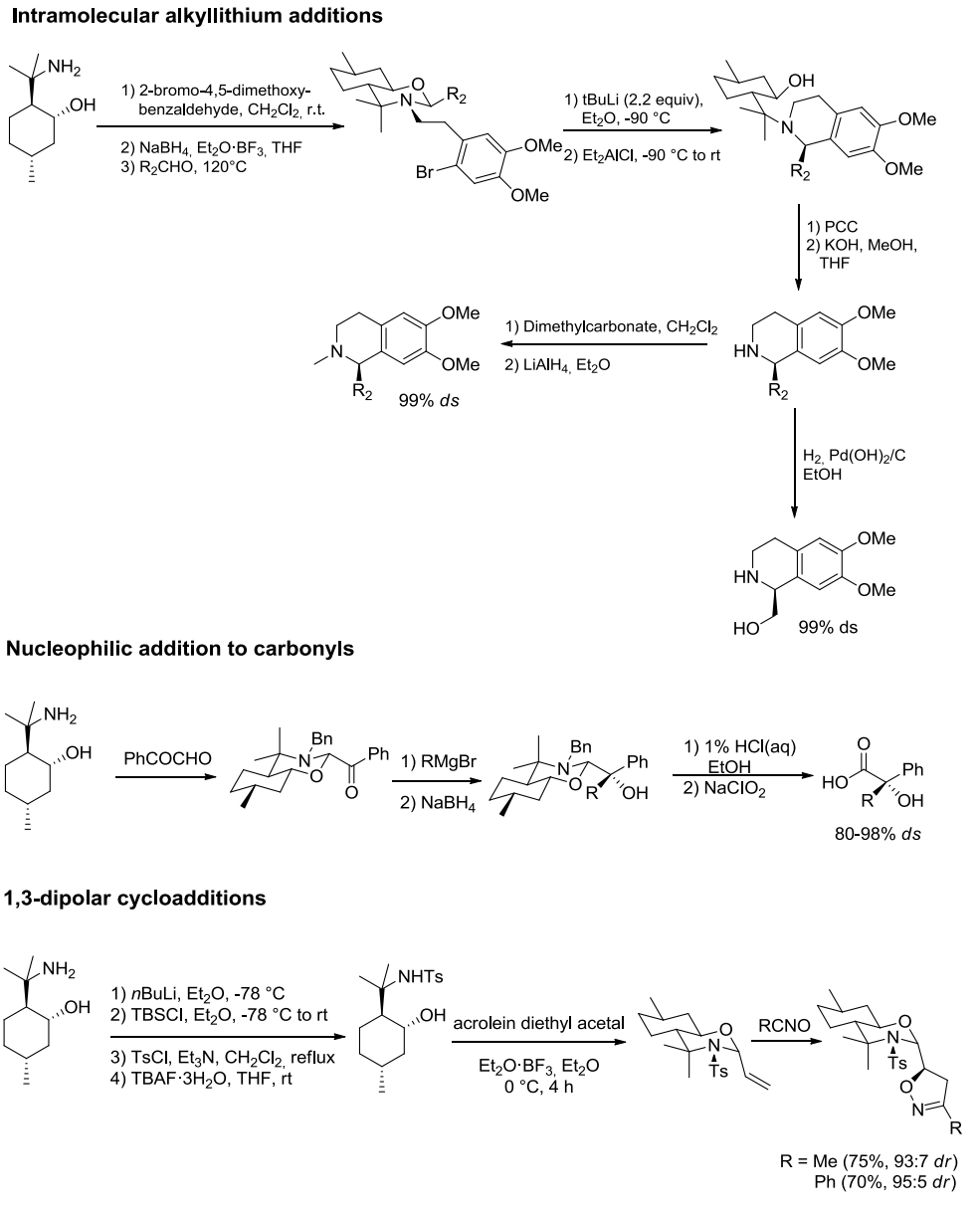
β–amino alcohols have been employed as ligands for early transition metals to provide complexes where the metal is in a highly asymmetric context. [19]

While less abundant than the β–amino alcohols, γ-amino alcohols have also contributed significantly to the advancement of asymmetric synthesis. Many have found application as chiral ligands or auxiliaries in a similar way to the β–amino alcohols but in different organic reactions. [20] Some of them are: ring opening reactions, addition reactions to carbonyls, pericyclic reactions, transition-metal-catalyzed reactions and radical cyclizations.

The majority of them are derived from common natural products such as menthol, camphor or sugars. 8-aminomenthol is very easy to preparate from commercially available (+)-pulegone [21] (Sheme 1.6) and can be applied for intramolecular alkyllithium additions, [22] nucleophilic addition to carbonyls, [23] and 1,3-dipolar cycloadditions [24] with high control of the enantioselectivity (Scheme 1.7).



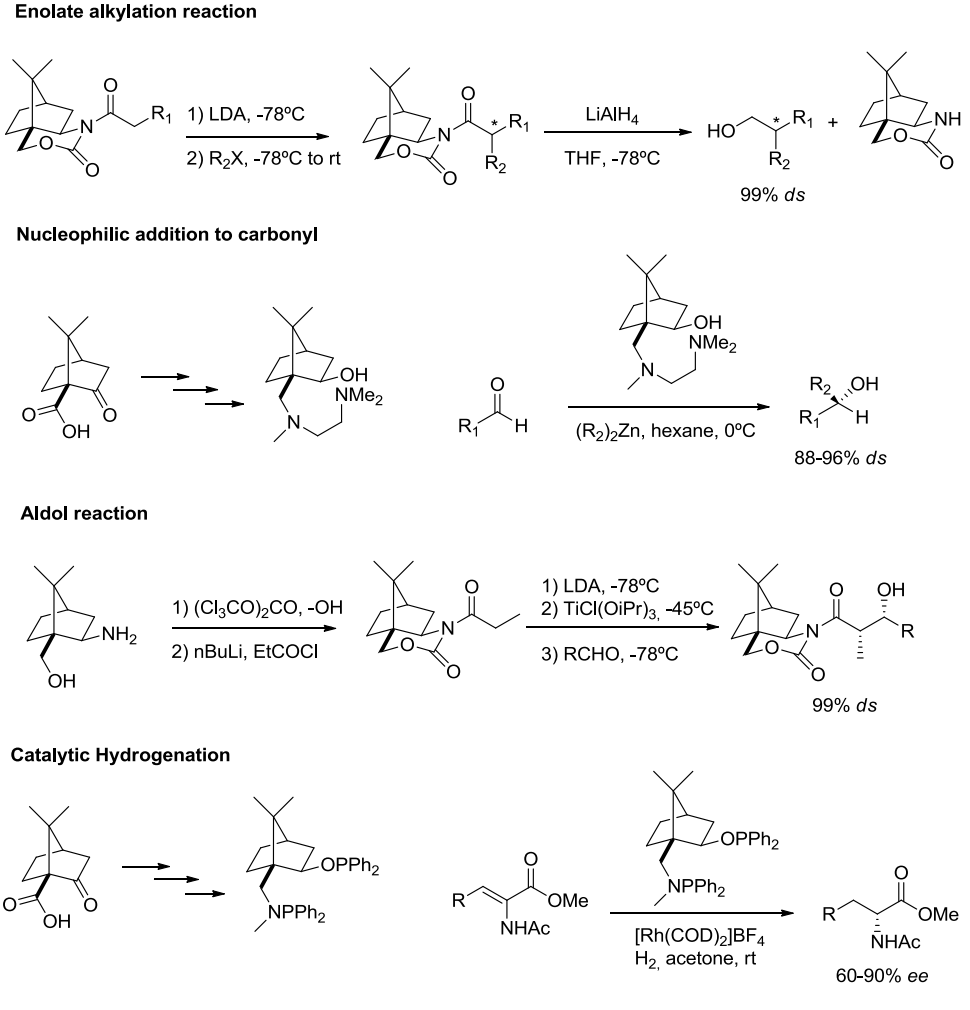
Scheme 1.6 Synthesis of 8-aminomenthol.



Scheme 1.7 Application of 8-aminomenthol in asymmetric organic reactions.

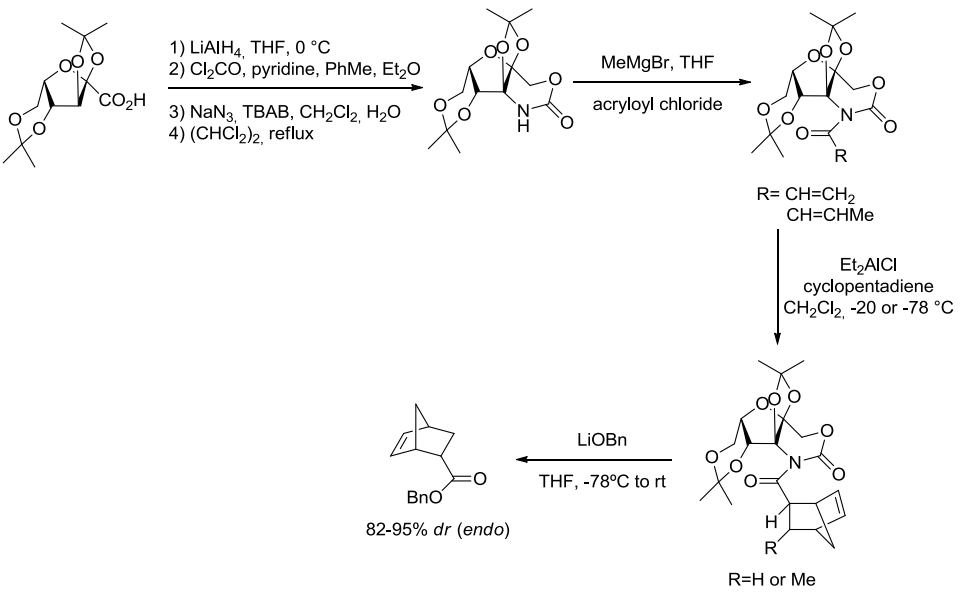
Camphor-based amino alcohols have been used as auxiliaries for enolate alkylations reactions, [25] nucleophilic addition to carbonyls, [26] and aldol

reactions; [27] or as skeletons for phosphine ligands and eventually they have been used in catalytic hydrogenation (Scheme 1.8). [28]



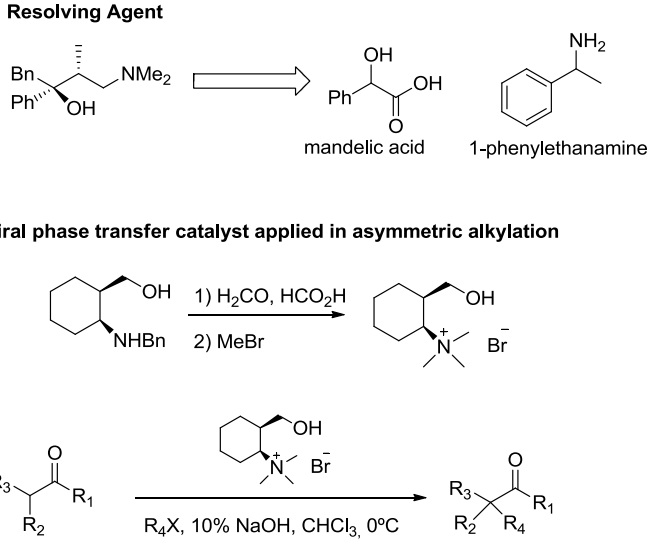
Scheme 1.8 Camphor derivatives used as chiral auxiliary or ligand to induce chirality.

The well-known Lewis-acid-catalyzed Diels-Alder reactions can also involve 1,3-aminated sugars as precursors of dienophiles (Scheme 1.9). [29]



Scheme 1.9 Sugar derivatives used in Diels-Alder reactions.

Moreover, they can be used as a resolving agent, [30] and as a phase transfer catalyst (Scheme 1.10). [31]



Scheme 1.10 Amino alcohols used as resolving agent (on the top) or chiral phase transfer agent in catalytic alkylations (on the bottom).

c) Natural and biological products:

The amino alcohols are found in a large variety of biologically important compounds.

The β–amino alcohols are the most common compounds found in natural or biological compounds due to the fact that they are intrinsically part of β–hydroxyl-α-amino acids. For instance, the antifungal agent sphingofungin [32] contains a hydroxyl amino acid moiety in the polar head group and the vancomycin [33], a class of antibiotics, contains an arylserine moiety (Figure 1.7).

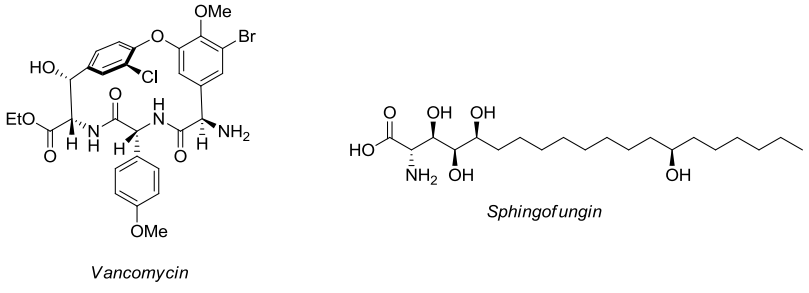


Figure 1.7 Structures of some biologically active β–amino alcohols.

The cyclic β–amino alcohols constitute also a large group of biologically active natural products. For example, the quinine that is used for malaria treatment [34]. One important class is the polyhydroxylated alkaloids, also known as aza-sugars. They can be potent inhibitors of α– and β– glucosidases as in the case of (+)-castanospermine drug (Figure 1.8). [35]

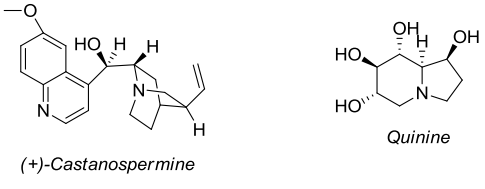


Figure 1.8 Cyclic β–amino alcohols used as biological active natural products.

Pharmacologically active β–amino alcohols are very common as peptidomimetics compounds. Their structures are similar to the natural peptides that allow them to

interact with the corresponding target. For example, Saquinavir is used in Renin or HIV-1 protease inhibition (Figure 1.9). [36]

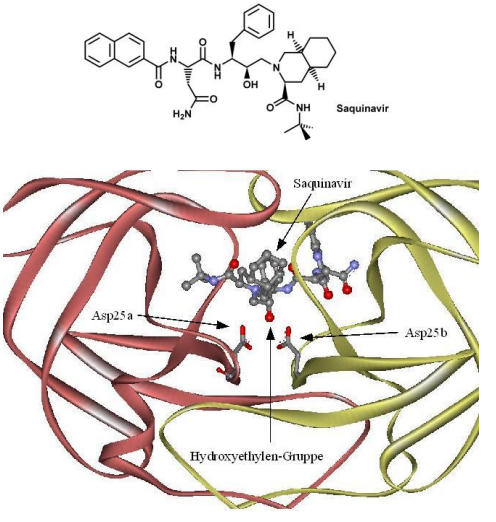


Figure 1.9 The structure of Saquinavir mimic the target of HIV-1 protease.

The γ–amino alcohol moieties are rare to be found directly in natural products, however, some natural products can be precursor of them. For example, fingolimod [37] is a synthetic compound based on the fungal secondary metabolite myriocin (ISP-I). It is a potent immunosuppressant used in multiple sclerosis (Figure 1.10). [38]

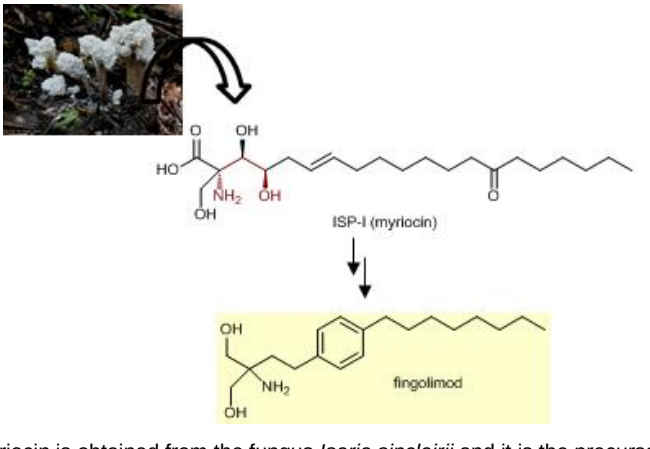


Figure 1.10 Myriocin is obtained from the fungus *Isaria sinclairii* and it is the precursor to obtain the potent immunosuppressant fingolimod.

In the last decades, the γ–amino alcohols have become increasingly important as pharmaceutical compounds. Negamycin is a derivative of a γ–amino alcohol that has a mechanism of action similar to that of most of the aminoglycosidic antibiotics including streptomycin and kanamcin; that is, negamycin causes inhibition of protein synthesis and misreading of the genetic code (Figure 1.11). [39]

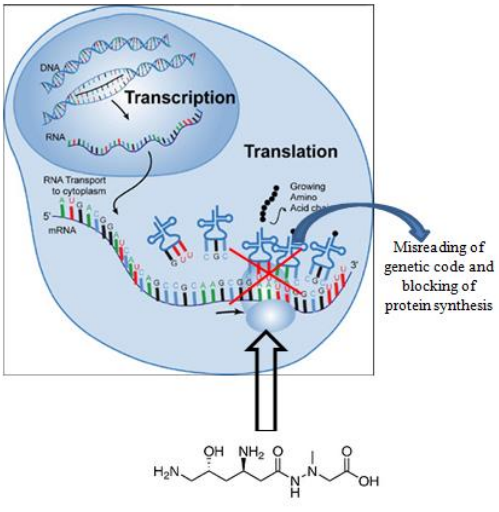


Figure 1.11 Effect of negamycin in gram negative bacteria.

Another example is the group of nikkomycins that are peptidyl nucleoside antibiotics. [40] They act as an inhibitor of chitin synthases in fungi and insects (Figure 1.12).

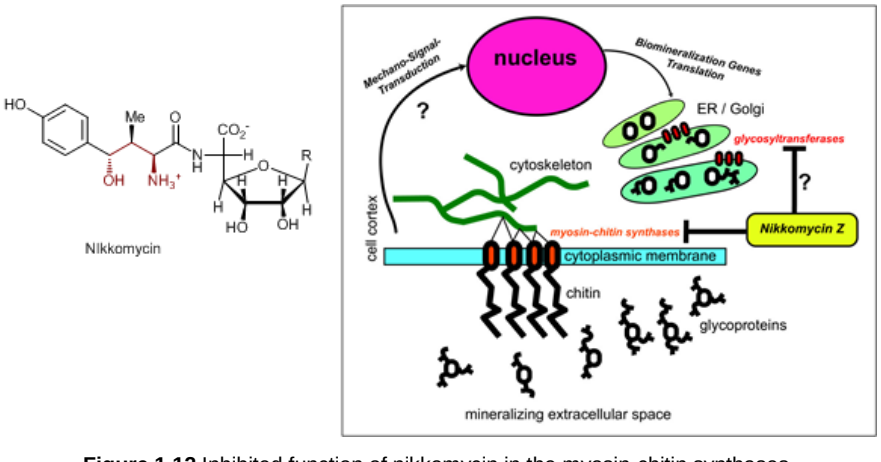


Figure 1.12 Inhibited function of nikkomycin in the myosin-chitin synthases.

Moreover, a new generation of antidepressant drugs from *MayoClinic* has an γ-amino alcohols functionality (Figure 1.13). [41]

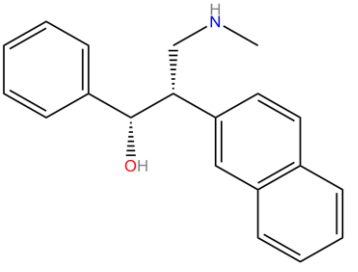


Figure 1.13 Structure of the antidepressant drug PCR200_structure.

Remarkably, the 1,3-*syn*-amino alcohol functionality is the key element for some HIV-protease inhibitors as ritonavir [42] and lopinavir (Figure 1.14). [43]

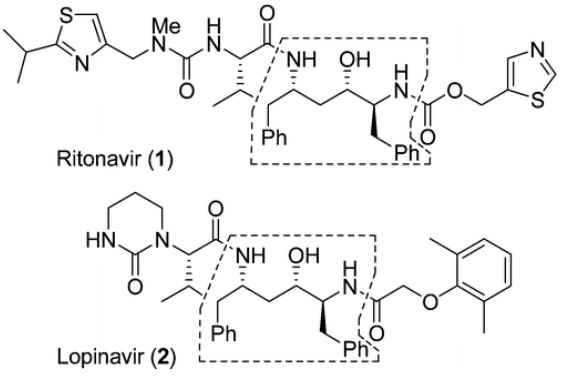


Figure 1.14 1,3-*syn*-amino alcohols inhibitors of HIV-protease.

The chirality in the amino alcohols represents a key function in many bioactive amino alcohol structures. For example, both the γ–amino alcohols (*R*)-procyclidine and (*R*)-trihexyphenidyl are among the most effective anticholinergic agents used for the treatment of Parkinson's diseases in which the absolute configuration is essential for their pharmacological activities (Figure 1.15). [44] Consequently, the chiral control of their synthesis has a high priority from the context of medicinal chemistry and drug discovery.

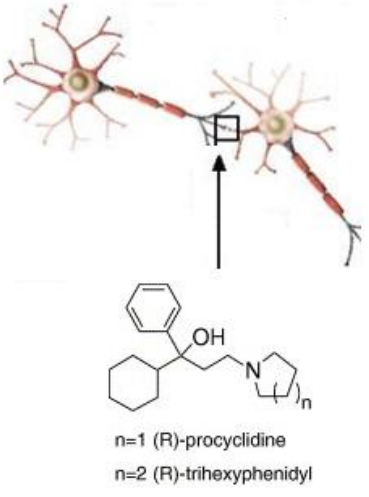


Figure 1.15 (*R*)-procyclidine and (*R*)-trihexyphenidyl are the enantiomers that can efficiently bound in dopamine receptors to improve synapses connection when dopamine concentration is low (Parkinson illness).

Considering the numerous and highly important applications of β– and γ– amino alcohols, it is not surprising that considerable attention has been devoted to their stereoselective synthesis.

1.2 Synthetic routes towards chiral amino alcohols

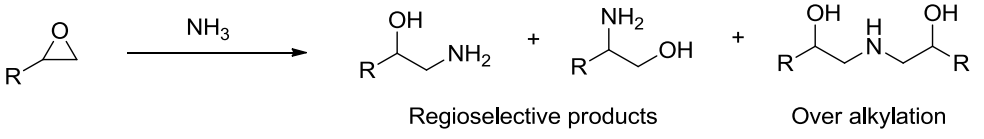
The synthetic routes towards enantiopure amino alcohols traditionally have mainly been related on the derivatization of chiral amino acids, with the inherent limitation of accessible targets. To avoid these drawbacks, considerable efforts have been made to develop alternative routes towards chiral amino alcohols, which can be divided into two strategically different approaches:

- The amino alcohol functionality can be introduced on a pre-existing carbon skeleton.
- The formation of a new carbon-carbon bond and that of one or two of the stereogenic centers in one single step.

The most important routes to the synthesis of the β– and γ– amino alcohol will be discussed in the following section.

1.2.1 β–Amino alcohols

The most common route towards enantiomerically enriched β–amino alcohols is based on the nucleophilic ring opening of epoxides using amines as nucleophiles. [45] This approach can be used in the synthesis of both *syn*- and *anti*- β-amino alcohols due to the fact that *cis*- and *trans*- epoxides are commercially available in high enantiomeric purity. However, the regioselectivity of the reaction is frequently poor and over alkylation of the nucleophile can also take place (Scheme 1.11).

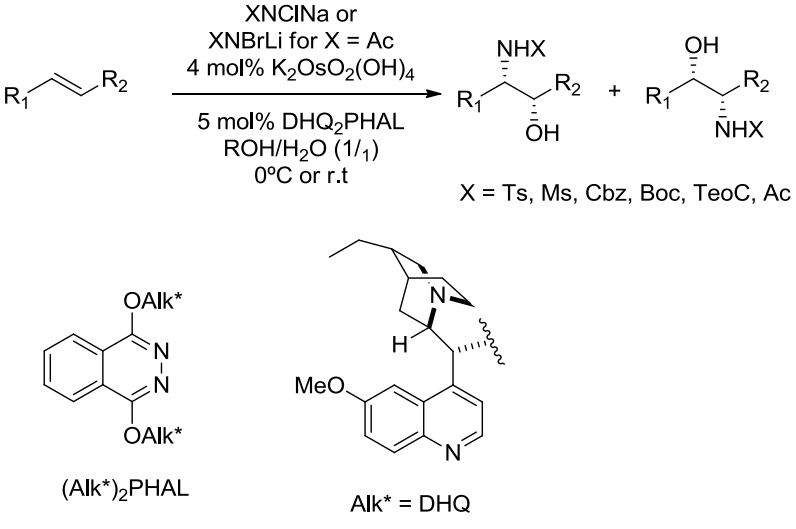


Scheme 1.11 Opening of epoxides with nitrogen nucleophiles towards β–amino alcohols.

The β–amino alcohols can also be obtained through ring-opening of other cyclic substrates such as aziridines, [46] sulfates, [47] and carbonates, [48] but there are also drawbacks in the regioselectivity.

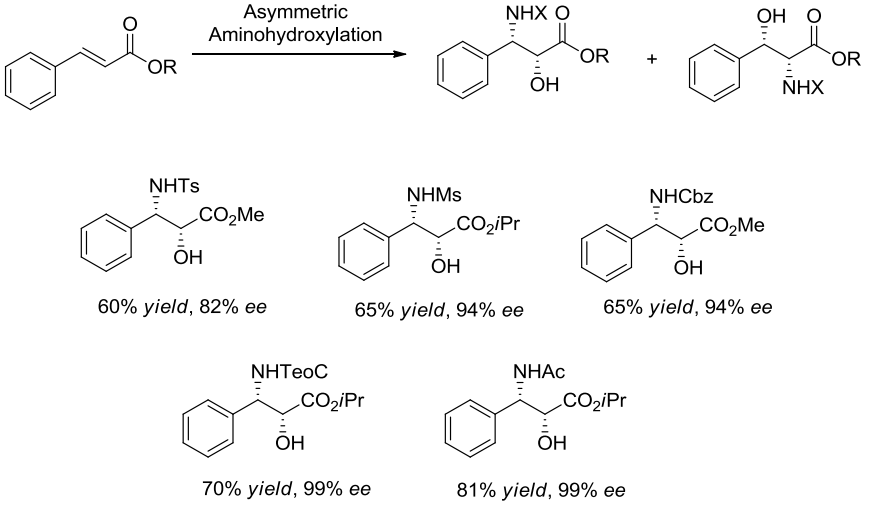
For these reason, the most direct approach towards the enantioselective synthesis of β-amino alcohols is the Sharpless asymmetric aminohydroxylation of alkenes. [49] Currently, there are six different methods available for carrying out asymmetric aminohydroxylations. They only differ in the N-protecting group that is introduced: *p*-toluenesulfonyl (Ts), [49] methanesulfonyl (Ms), [50] benzyloxycarbonyl (Cbz), [51] *tert*-butoxycarbonyl (Boc), [52] 2-trimethylsilylethoxycarbonyl (TeoC), [53] or acetil (Ac). [54] Each method uses a combination of osmium tetraoxide, alkaloid-derived ligands and the Li or Na salt of an N-halogenated sulfonamide, alkyl carbamate or amide in an alcohol/water solvent mixture (Scheme 1.12). Two regioisomers can be produced from an

unsymmetrical alkene and is often difficult to control the regioselectivity, for this reason, the yields of the reactions are usually moderate.



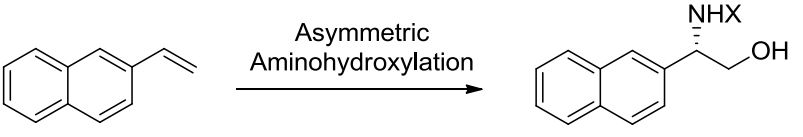
Scheme 1.12 Overview of Sharpless asymmetric aminohydroxylation.

Cinnamates have been proved to be one of the most successful types of alkene substrates for the Sharpless asymmetric aminohydroxylation with high control of the diastereoselectivity (Scheme 1.13). [55]



Scheme 1.13 Asymmetric aminohydroxylation of cinnamates.

In contrast, α,β-unsaturated esters and vinyl arenes were not initially successfully aminohydroxylated. It was only with the advance of the carbamate- and acetamide-based processes that such compounds became accessible. [52] The regioselectivity for styrenes is found to be dependent on the nature of the ligand, the solvent and the N-protecting group introduced (Scheme 1.14).

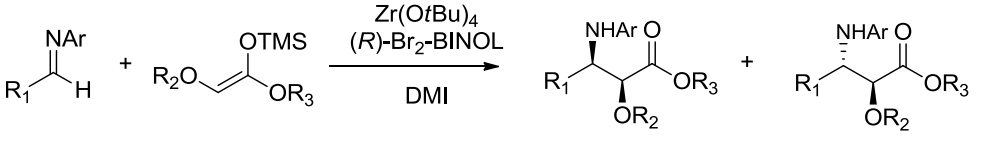


X = Cbz: 71%; 94% *ee*
TeoC: 70%; 98% *ee*
Boc: 76%; 97% *ee*

Scheme 1.14 Asymmetric aminohydroxylation of 2-vinyl naphthalene.

During the last years, a number of significant advances in the asymmetric Sharpless aminohydroxylation have been described. However, some issues, such as lack of regioselectivity and poor substrate scope in certain cases, need to be resolved. [56]

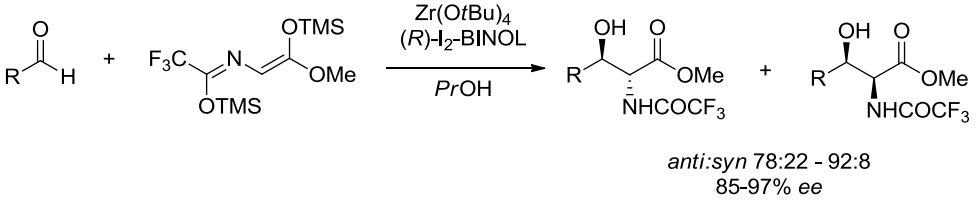
The amino alcohol moiety can also be constructed by coupling two fragments, one containing the oxygen functionality and one containing the nitrogen functionality. One elegant example is the stereoselective Mannich-type reaction. [57] It is based on nucleophilic additions of α–alkoxy enolates to imines affording β–amino alcohols with high to excellent enantioselectivity (Scheme 1.15). [58]



syn:anti > 99:1 - 6:94
76-98% *ee*

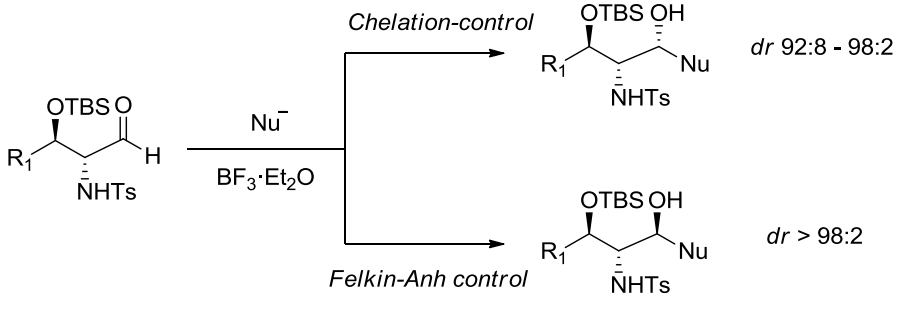
Scheme 1.15 Enantioselective Mannich reaction approach.

The Lewis acid-catalyzed aldol reaction is another route to synthesize β–amino alcohols. An example is zirconium/BINOL-catalyzed reactions of glycine derivatives and aldehydes to obtain anti-β-hydroxy-α-amino acids in excellent yields and enantioselectivities (Scheme 1.16). [59]



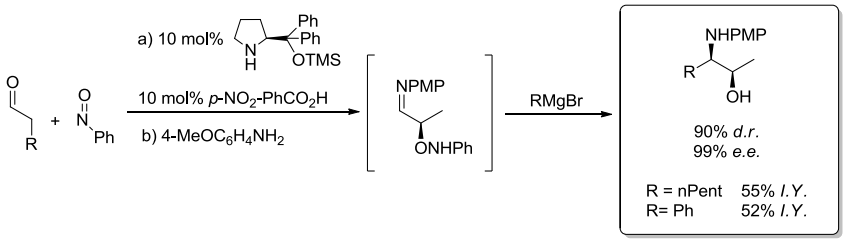
Scheme 1.16 Enantioselective aldol reaction to synthesize β–amino alcohols.

Another approach is the nucleophilic addition to chiral α-amino aldehydes where the preexisting stereogenic center is the key factor to obtain high control of the diastereoselectivity. Recently, Somfai and coworkers [60] designed a divergent protocol for substrate-controlled diastereoselective synthesis of amino diols based on nucleophilic Mukaiyama aldol additions to α–amino-β-silyloxy aldehydes (Scheme 1.17).



Scheme 1.17 Nucleophilic addition to chiral compounds by Chelation or Felkin-Anh control to obtain chiral aminodiols.

In the last year, a new approach based on the asymmetric *O*-nitroso aldol reaction of aldehydes catalyzed by α,α–diphenylprolinol trimethylsilyl eter has been developed. [61] The reaction provided α–oxyaldehyde adducts that were transformed in *situ* into α–oxyimines and after treatment with Grignard reagent, they were able to synthesize enantioenriched β–amino alcohols with good yields (Scheme 1.18).



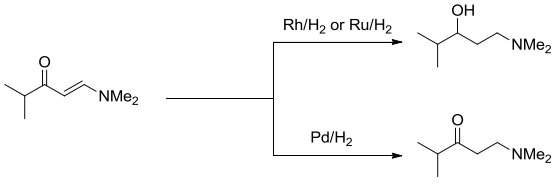
Scheme 1.18 β-amino alcohols from a nitroso aldol reaction, imine formation and Grignard addition sequences.

1.2.2 γ–Amino alcohols

The γ–amino alcohol synthesis commonly involves reductions by using metal hydride or using catalytic hydrogenation of 1,3-difunctionalited compounds with nitrogen and oxygen in the structure. This reduction can be divided according to the nature of 1,3-difunctionalitzated compound: enaminones, isoxazoles or isoxazolines, β-amino carbonyl compounds or ketopyridines.

a) Reduction of enaminones:

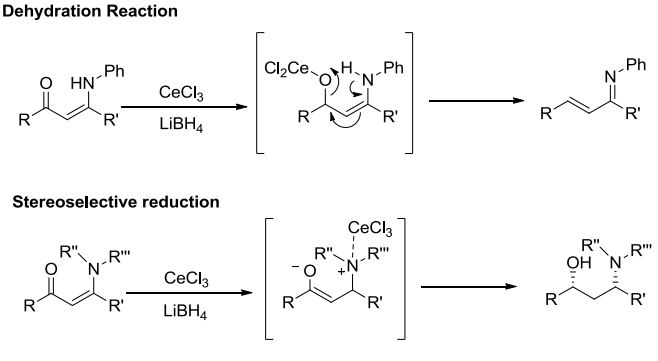
In many examples investigated, the standard techniques fail to give any reaction and under more forcing conditions either nitrogen [62] or oxygen, [63] is removed from the molecule. However, these compounds can be reduced in low yields to γ–amino alcohols by catalytic hydrogenation. Over palladium, the hydrogenolysis gives the neutral ketone but over rhodium or ruthenium the saturated amino-alcohol can be formed (Scheme 1.19). [64]



Scheme 1.19 Reduction of enaminones under catalytic hydrogenation.

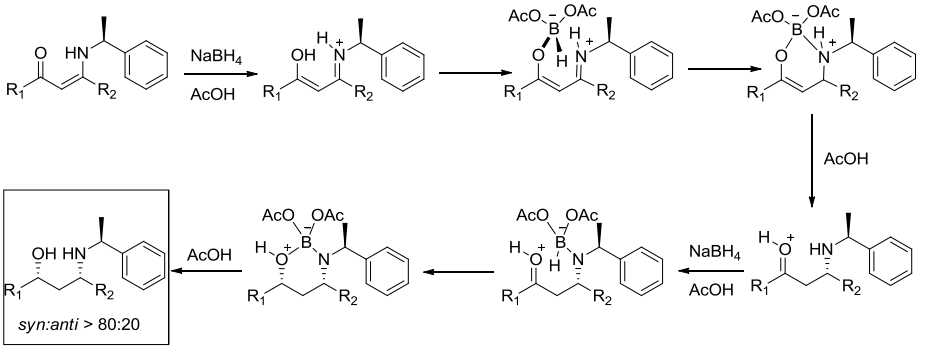
Palmieri and coworkers [65] have studied both the regioselective synthesis of enaminones and their dianion reactivity to find out that the reduction of the enaminone by sodium in isopropanol takes place with difficulty and reduction with metal hydrides alone afforded low conversions but moderate to high diastereoselectivities.

However, Tagarelli and coworkers [66] explored the reduction by borane complexes or $LiBH_4$ in the presence of $TiCl_4$ and $CeCl_3$ to obtain high yield (70-96%) and high diastereoselectivities into the *syn* product (up to 86% *ds*). From a mechanistic point of view, the most remarkable finding was a strong dependence of the chemoselectivity from the nitrogen substituent. They have found that a phenyl group linked to the nitrogen atom favours a dehydration reaction to form the α,β–unsaturated imine. On the other hand, an alkyl nitrogen substituent favours cerium co-ordination to nitrogen atom allowing 1,4-addition to the unsaturated carbonyl moiety (Scheme 1.20).



Scheme 1.20 The nature of the nitrogen substituents determines the chemoselectivity, resulting in a dehydratation reaction or in the stereoselective reduction of enaminones to *syn* 1,3-amino alcohols.

Recently, Palimieri and coworkers studied the chiral reduction of β–enamino ketones with sodium borohydride in acetic acid. [67] They were successful to obtain *syn* γ–amino alcohols with high diastereoselectivities (Scheme 1.21).



Scheme 1.21 Stereoselective synthesis of γ–amino alcohols by reduction of chiral β-enaminoketones with sodium borohydride.

Moreover, it is worth mentioning that molecular modelling studies justified the mechanistic proposal for the control of the diastereoselectivity (Figure 1.16).

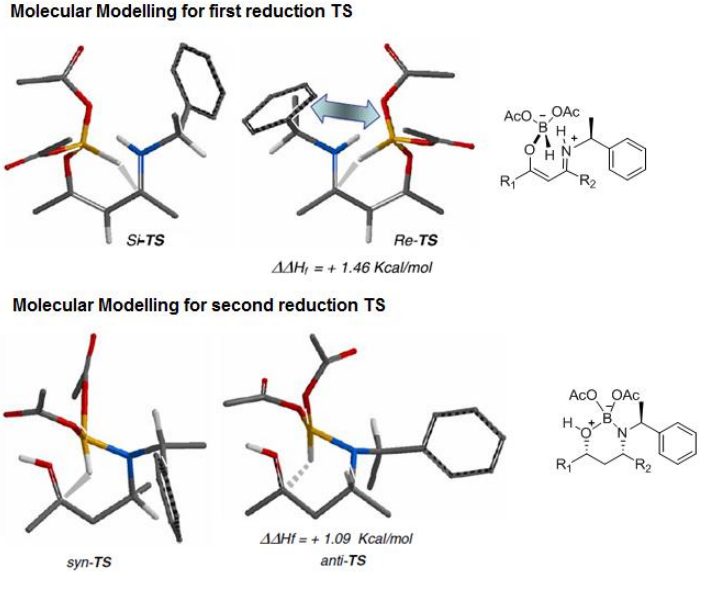
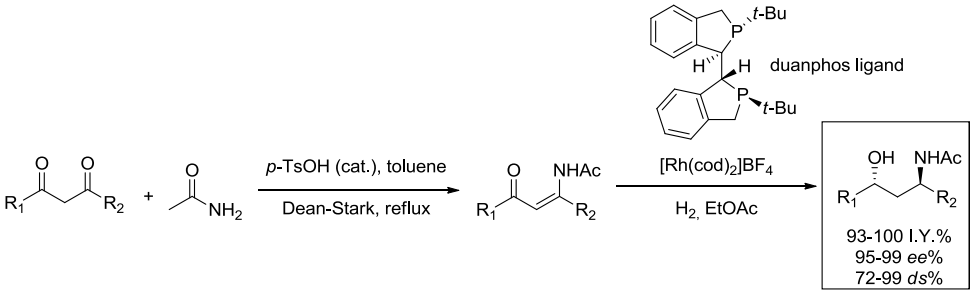


Figure 1.16 Molecular modelling representation of the diastereoselective transition states (TS) for the two reduction steps.

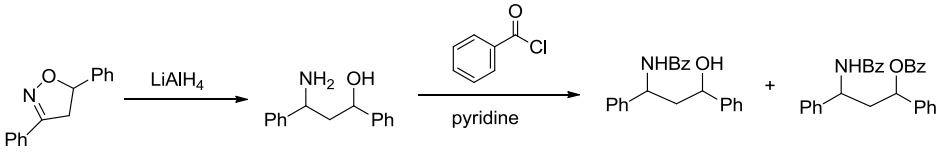
The latest advances in this area were the rhodium-catalyzed enantioselective and diastereoselective hydrogenation of enaminones developed by Zhang and coworkers. [68] They have prepared a scope of enaminones through condensation of the corresponding ketones and acetamides. Furthermore, they designed a rhodium catalytic system with highly electron-donating chiral phosphorus ligands to obtain *anti* 1,3-amino alcohols *via* asymmetric hydrogenation of the substrates (Scheme 1.22).



Scheme 1.22 Rhodium-catalyzed asymmetric hydrogenation of enaminones to form enantioenriched *anti* γ–amino alcohols.

b) Reduction of isoxazoles or isoxazolines:

The first example was obtained by Stühmer and Heinrich with the reduction of 3,5-diphenyl-2-isoazoline with sodium amalgam or by catalytic hydrogenation to give a mixture of the two diastereoisomeric 1,3-diphenyl-3-aminopropanols. [69] Later on, Reiche and coworkers used lithium aluminum hydride [70] to obtain 1,3-diphenyl-3-aminopropanol and the corresponding mono or di-benzoyl derivatives (Scheme 1.23). However, it was demonstrated the facile ring-opening of the isoxazoline ring to gave the amino alcohol.



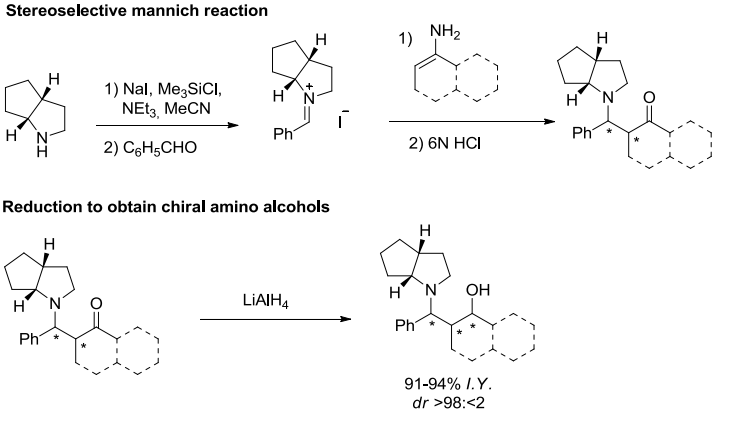
Scheme 1.23 Reduction of isoxazoline by lithium aluminum hydride to obtain γ–amino alcohol and benzoyl derivatives.

Moreover, Lunn used nickel-aluminum in potassium hydroxide solution to reduce isoxazoles in 75% of yield. [71] The reaction is simple to carry out and does not require special conditions or hydrogen atmosphere although it was found that the reaction frequently exhibited an induction period.

c) Reduction of β–amino carbonyl compounds:

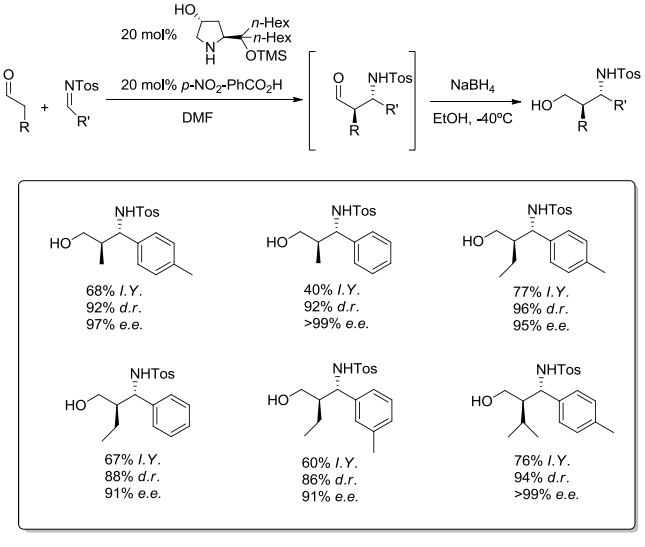
Originally, Andrisano and coworkers were able to reduce the α–chiral-β-aminopropiophenones by lithium aluminium hydride in a stereospecific way to afford the *syn* amino alcohol as the predominant diastereoisomer. [72] As another example, Barluenga and coworkers used the same reducing agent ($LiAlH_4$) to obtain amino alcohols with three centers of chirality with very good yields (83-97%). [73] They observed that the diastereoisomeric ratio depends on the reaction conditions and on the N-substituent in the substrate. The β–dialkylaminopropiophenones have also been asymmetrically reduced with (-)-bornan-2-exo-yloxyaluminium dichloride to the corresponding γ-amino alcohol in 58-92% enantiomeric excess. [74]

Martens and coworkers [75] used chiral heterocyclic amines to obtain diastereoselective β–amino ketones by a one-pot Mannich reaction and their subsequent reduction afforded sterically congested enantiomerically pure γ–amino alcohols (Scheme 1.24).



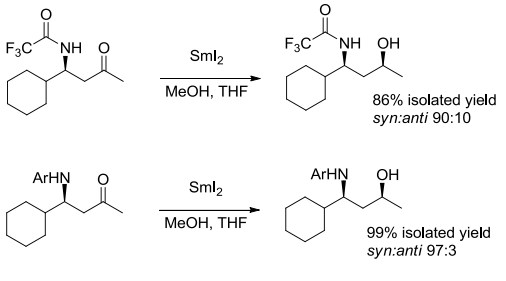
Scheme 1.24 Diastereoselective synthesis of β–amino ketones *via* Mannich reaction and their reduction to chiral 1,3-amino alcohols.

Another example is the 4-hydroxypyrrolidine-catalyzed Mannich reaction of aldehydes optimized by Palomo and coworkers. [76] They reported a highly efficient catalytic system for the *anti*-selective Mannich reaction of aldehydes with N-sulfonyl imines followed by the reduction of the mannich adducts to obtain chiral γ–amino alcohols (Scheme 1.25).



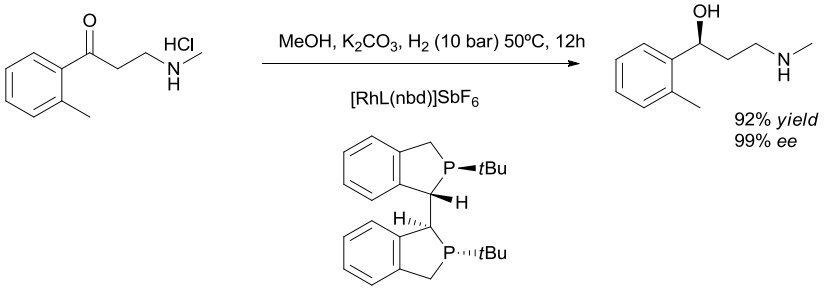
Scheme 1.25 Catalytic asymmetric Mannich reaction followed by reduction to chiral γ–amino alcohols.

In the last decade, new reduction methods have been developed to obtain high control of diastereoselectivity. One example is the work of Truong and coworkers. [77] They directly reduced β–amino ketones to *syn* or *anti* γ–amino alcohols with SmI_2 due to a divergence in selectivity with different N-protecting group (Scheme 1.26).



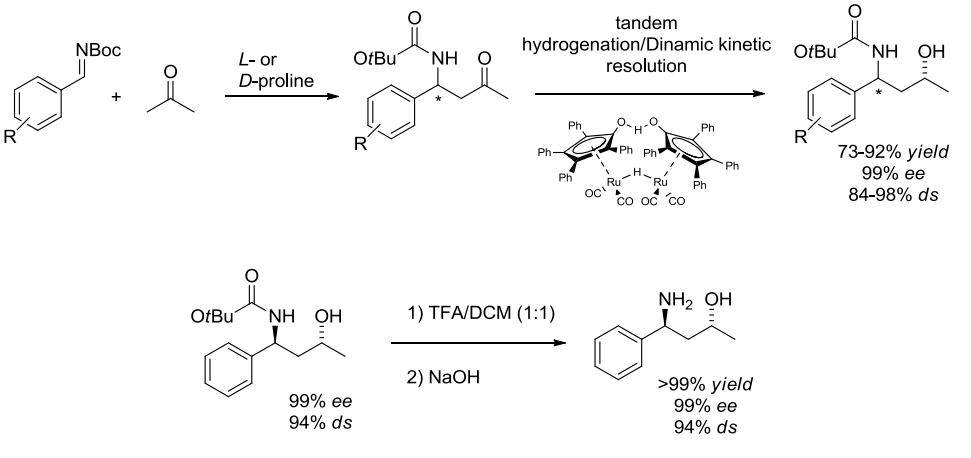
Scheme 1.26 The different N-protecting group is the key element for the control of the diastereoselectivity.

Zang and coworkers used rhodium catalyzed hydrogenation to reduce β–secondary amino ketones with total control of enantioselectivity (Scheme 1.27).



Scheme 1.27 Rhodium-catalyzed asymmetric hydrogenation of β–secondary amino ketones.

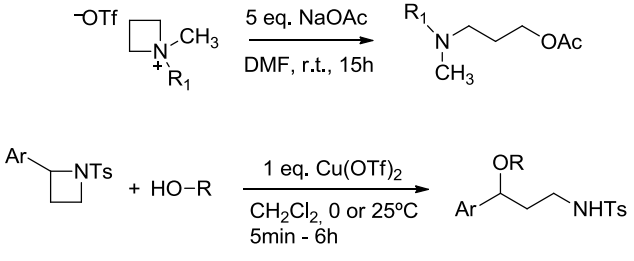
One of the latest approaches is a two-step procedure which combines organo-, organometallic, and enzymatic catalysis developed by Bäckvall and coworkers. [78] They synthesized enantiopure β–aminoketones *via* organocatalysis which were subjected to reduction and subsequent dynamic kinetic asymmetric resolution to give enantio- and diastereomerically pure 1,3-aminoacetates. Hydrolysis of the acetate was carried out without any loss of enantio- or diastereoselectivity (Scheme 1.28).



Scheme 1.28 Enantioselective synthesis of *syn*- and *anti*-1,3-amino alcohols via β–aminoketones and subsequent reduction/dynamic kinetic asymmetric transformation.

Another possibility is the reduction of ketopyridines although only one example is found in the literature. [79]

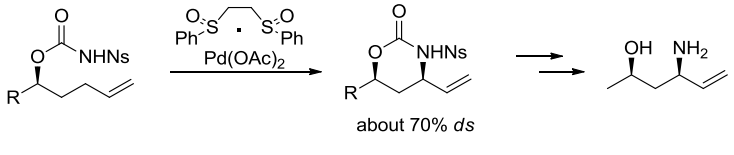
Recently, two different synthetic methods based on ring-opening of azetidines have been developed. Vargas and coworkers reported interesting insights into the regioselectivity of the ring-opening with an array of nitrogen (azide anion or benzylamine) and oxygen (acetate anion or alkoxides) nucleophiles with control of the regioselectivity. [80] Lewis acid-mediated highly regioselective S_N2-type ring-opening of 2-aryl-N-tosylazetidines with alcohols was described by Shukla and coworkers. It afforded various 1,3-amino ethers in excellent yields with good enantiomeric excesses (Scheme 1.29). [81]



Scheme 1.29 Ring-opening to synthesize γ–amino alcohols.

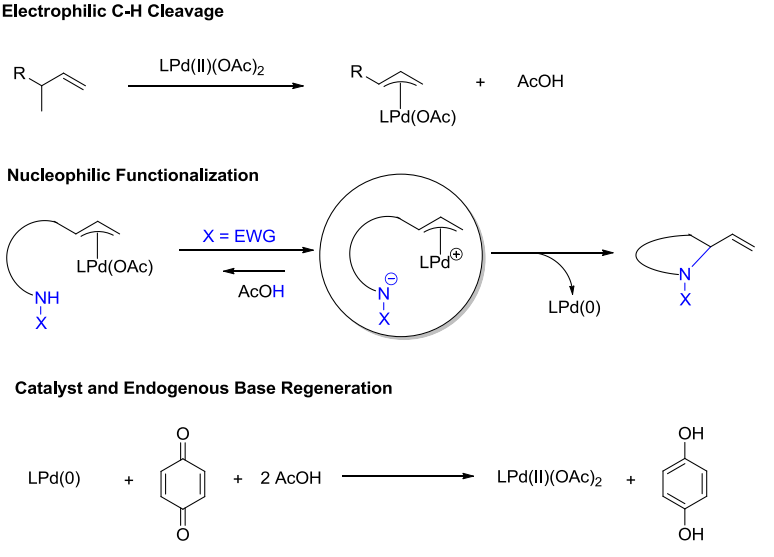
The ring-opening of azetidinones can also be an interesting method to obtain β–amino ketones and, after reduction of the carbonyl group, the desired γ-amino alcohol. [82]

In the last years, allylic C-H amination methods have been developed for the preparation of chiral γ–amino alcohols. Initially, White and coworkers [83] reported a palladium catalyst to obtain a range of different *syn*-1,3-amino alcohol (Scheme 1.30).



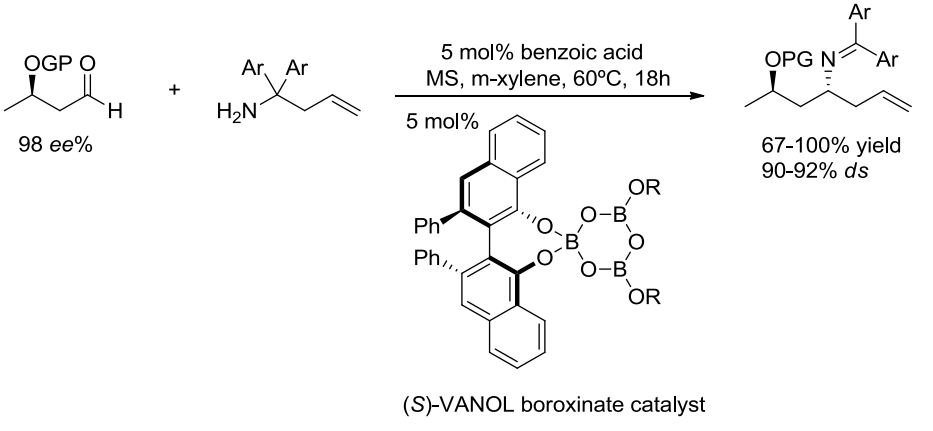
Scheme 1.30 Palladium-catalyzed C-H allylic activation to obtain *syn*-γ-amino alcohols.

They described the mechanism along three steps: electrophilic C-H cleavage, nucleophilic functionalization and catalyst regeneration (Scheme 1.31).



Scheme 1.31 Key steps in the mechanism of palladium-catalyzed allylic C-H amination.

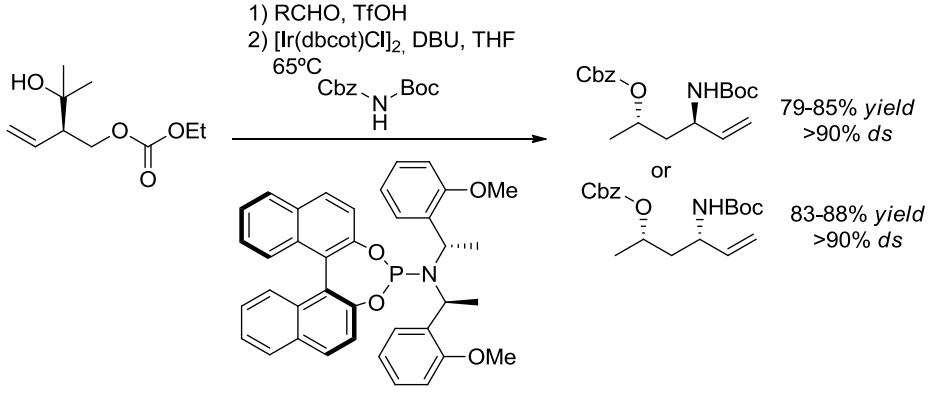
More recently, the catalytic asymmetric aminoallylation of chiral aldehydes has been developed as a new method for the catalytic synthesis of *syn* and *anti* 1,3-amino alcohols (Scheme 1.32). [84]



(*S*)-VANOL boroxinate catalyst

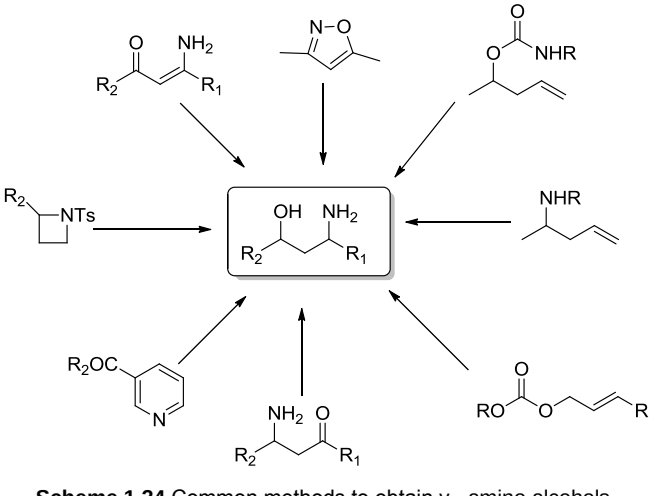
Scheme 1.32 The use of (*S*)-VANOL boroxinate catalyst to control the stereoselectivity in the catalytic aminoallylation of chiral aldehydes.

Han and coworkers [85] have found novel chiral bifunctional reagents which are air-stable and can be used in a step-economical fashion. The reagents afforded asymmetric aldehyde allylation followed by Ir(I)-catalyzed allylic amidation to deliver protected *syn*– and *anti*– 1,3-amino alcohols in good yields (79-88%) with excellent stereoselectivities (>90%) (Scheme 1.33).



Scheme 1.33 Ir(I)-catalyzed diastereoselective allylic amidation of homoallylic alcohols.

In summary, the common methods to synthesize γ–amino alcohols are reductions with metal hydrides or catalytic hydrogenation of enaminones, isoxazoles or isoxazolines, β-amino carbonyl compounds, ketopyridines, ring opening of azetidines or allylic reactions (Scheme 1.34).

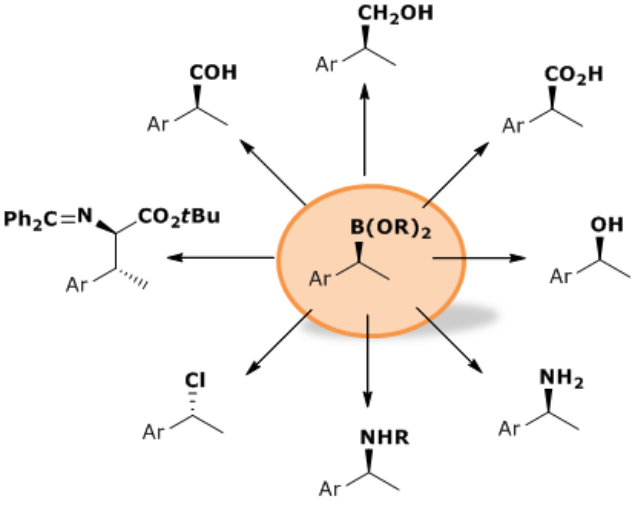


Scheme 1.34 Common methods to obtain γ– amino alcohols.

Despite the fact that a large number of synthetic routes have been developed to prepare amino alcohols, some limitations on the nature of the substrate and reagents can be found. Consequently, an alternative method that accomplishes the required requisites and become economically attractive is still a challenge.

1.3 Organoboron compounds in organic synthesis

One of the most important applications in boron chemistry is the synthesis of organoboranes. They can be utilized in biomedical sciences, for instance as ^{10}B carriers for neutron capture therapy [86] and as well as biologically active compounds [87]. They are also of great interest in synthetic organic chemistry as functional molecules [88] and functional polymers [89]. Moreover, the C-B bond can be considered as an ideal platform to introduce functionalities. It can be transformed into C-O, C-N, C-C and C-X bonds having the configuration retained in the functionalization process (Scheme 1.35). [90]



Scheme 1.35 Examples of transformations of C-B bond.

Among the organoborane compounds, the most frequently used in synthesis are the organoboronic esters for three reasons:

a) High stability:

The partial donation of the lone pair of electrons of the oxygen atoms into the empty *p*-orbital of the boron atom makes the boron atom less Lewis acidic, hence, the compounds easier to handle. But the stability of the organoboronic esters

towards hydrolysis depends on their particular structure (Figure 1.17). Thus, bulky, aliphatic and cyclic organoboronic ester compounds are, in general, easy to purify, to store and to handle. [91]

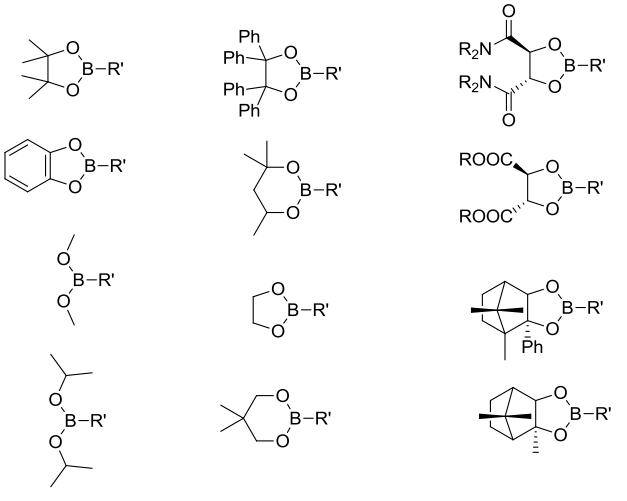
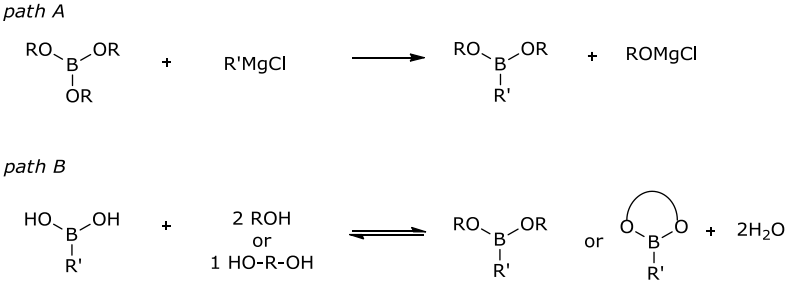


Figure 1.17 Palette of organoboronic esters.

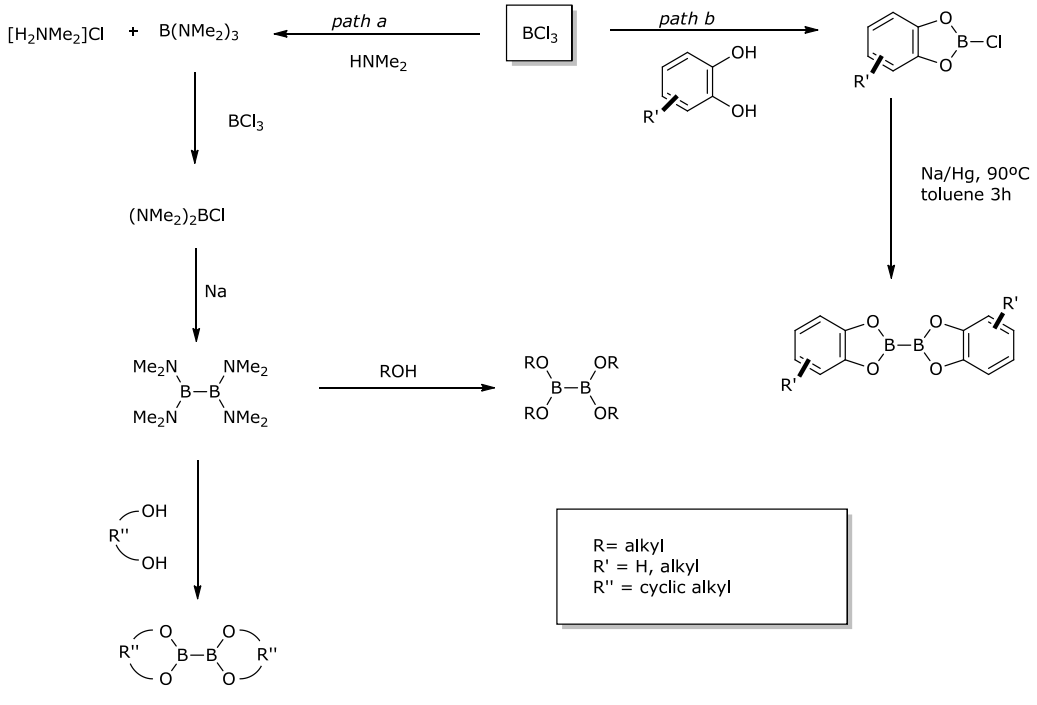
b) Easy accessibility:

A large scope of organoboronic esters are commercially available with low to moderate cost or they are easy to synthesize. They have traditionally been synthesized through transmetallation from organomagnesium or organolithium reagents [92] and trialkoxylboranes (Scheme 1.36). [93] While the sensitivity of the reagents and the extreme anhydrous conditions required for the reaction requires an alternative methodology: that is the esterification of organoboronic acids with the corresponding alcohols.



Scheme 1.36 General synthesis of organoboronic esters.

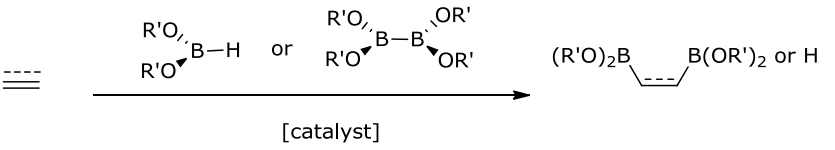
The synthesis of diboronic esters can involve multiple-step synthesis. One of the best established methodologies was developed by Noth [94] and improved by Marder [95] and Srebnik. [96] It involves the formation of a tris(alkylamino)borane as an intermediate (Scheme 1.37, *path a*). An alternative synthesis based on the reductive homocoupling of halocatecholboranes [97] was established by Hartwig and coworkers (Scheme 1.37, *path b*), but the method is not suitable for the synthesis of tetraalkoxydiborons.



Scheme 1.37 Synthetic routes towards diboron compounds.

c) Versatile reactivity:

Hydroboration, diboration or β-boration are the most common addition reactions of organoboronic esters to unsaturated organic compound. These methodologies provide alternative synthetic routes towards organoboron compounds (Scheme 1.38).



Scheme 1.38 Alternative synthetic routes towards organoboron compounds: addition of boron reagents to unsaturated substrates.

Taking into consideration the advantages of organoboronic esters in organic synthesis, new synthetic routes towards amino alcohols can be developed based on the catalytic β–boration of α,β–unsaturated compounds.

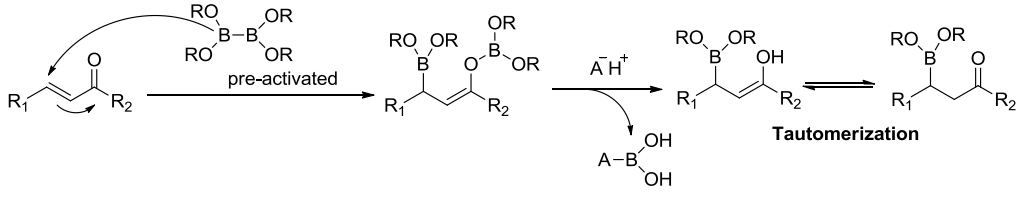
1.3.1 The background of the catalytic β–boration reaction

α,β-Unsaturated compounds exhibit unique reactivity towards nucleophilic addition of organometallic reagents. Organomagnesium or organolithium derivatives are most frequently used but they can tolerate only a few electrophilic groups, and therefore the use of functional group protection is often required. In this case, the diboron reagents can be a good alternative to use.

Formally, the reaction is a “hydroboration”, achieved with a tetraalkoxydiborane and a proton source as reagents. The addition of only one of the boron atoms of the diboron reagent makes the atom economy of the β–boration reaction obviously poor. However, the products are very attractive, desirable intermediates for a wide range of valuable chiral compounds. For this reason, this reaction is probably an essential synthetic tool in preparative organic chemistry and has been studied in depth.

The β–boration reaction needs the previous activation of the diboron reagent that can be performed by the use of transition metal complexes (oxidative addition or σ–bond metathesis) or *via* organocatalytic approaches. In general, the reaction proceeds by 1,4-addition of the diboron reagent to the C=C-EWG conjugated π–system, and the final product derives from the protic cleavage of the O-B bond

followed by the tautomerization of the borylated enol into the more stable keto-form (Scheme 1.39).

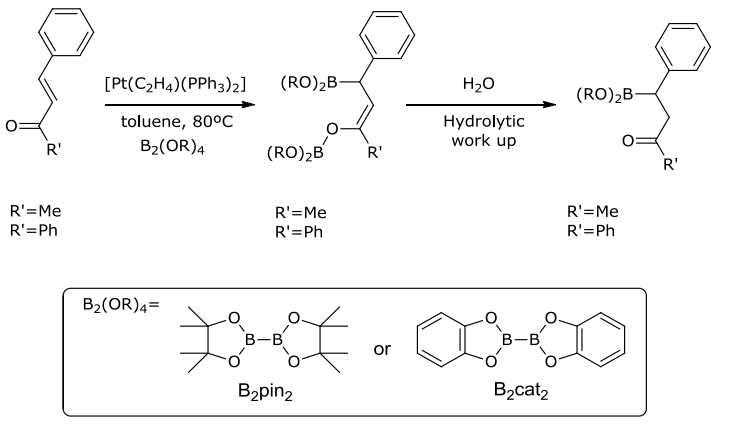


Scheme 1.39 β–Boration of electron deficient olefins.

1.3.2 Activation of diboron reagent by oxidative addition

The first β–boration reactions were carried out via activation of diboron reagents by oxidative addition to transition metals complexes, using platinum and rhodium complexes.

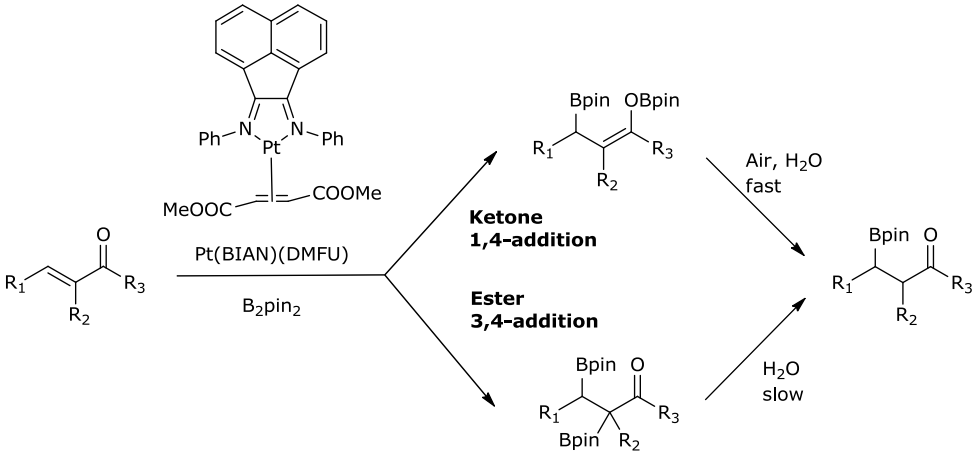
Marder and co-workers [98] studied the reaction of the diboron reagents B_2pin_2 and B_2cat_2 with α,β–unsaturated ketones in the presence of the Pt(0) catalyst, $Pt(C_2H_4)(PPh_3)_2$. They did not use a protic additive and were able to identify the 1,4-diborated intermediates which were sensitive to the exposure to water and readily formed the β–borated products. The two diboron reagents, B_2pin_2 (bis(pinacolato(diboron) and B_2cat_2 (bis(catecholato)diboron), reacted with similar activity and selectivity. The only difference was that the 1,4-diborated intermediates from B_2cat_2 were more susceptible to hydrolysis than those involving B_2pin_2 (Scheme 1.40).



Scheme 1.40 First catalytic β-boration reactions of α,β-unsaturated ketones.

Alternatively, Srebnik and co-workers [99] established a more general Pt mediated β–boration methodology, and increased the range of substrates by including cyclic enones, α,β-unsaturated esters and aldehydes.

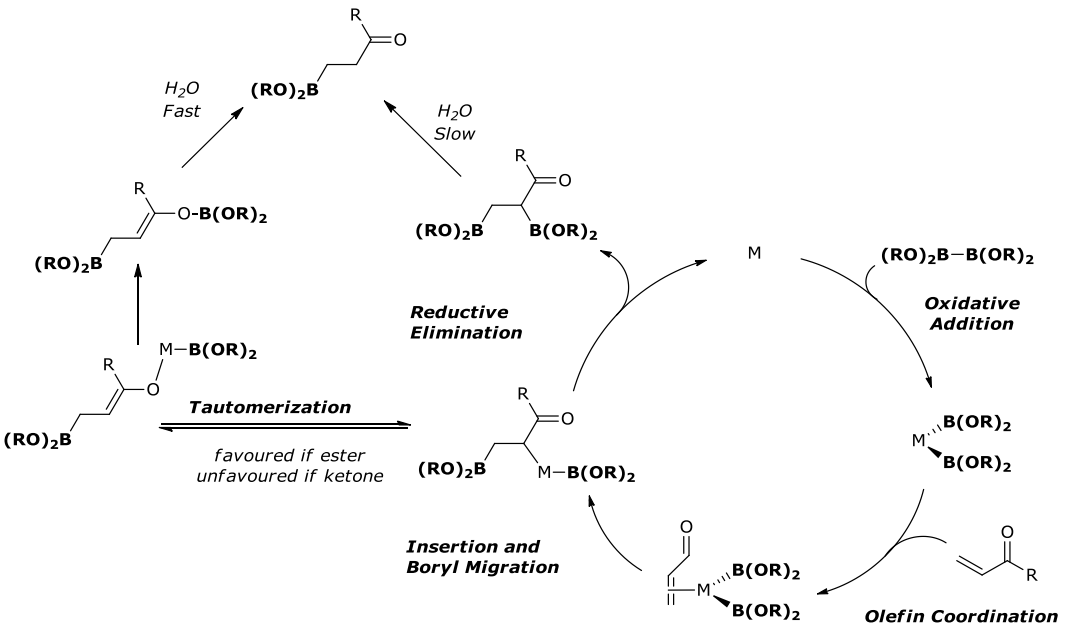
Marder and coworkers [100] observed that the second generation of platinum (0) catalyst, [Pt(BIAN)(DMFU)], was more active and all reactions could be performed at room temperature with good to excellent yields. Using this catalytic system, the different reactivity of ketones and esters described in the previous section was observed experimentally. α,β–Unsaturated ketones formed the expected 1,4-diborated intermediates while α,β–unsaturated esters formed the 3,4-diborated intermediates. Moreover, they observed that the C_α-B bonds were more stable when exposed to air but hydrolyzed slowly upon addition of water, whereas the C_β-B bonds were sensitive neither to oxygen nor to water. Thus, the hydrolysis of both types of intermediate leads to the corresponding β–borated products (Scheme 1.41).



Scheme 1.41 β-boration of α,β-unsaturated ketones and esters with second generation of Pt(0) catalysts.

Kabalka and coworkers [101] reported in 2002 that the Wilkinson catalyst, $Rh(PPh_3)_3Cl$, catalyzed the β-boration of a large scope of α,β-unsaturated carbonyl compounds (cyclic and acyclic ketones, esters, aldehydes and nitriles).

Considering the mechanism of these reactions, it has been hypothesized that the diboron reagents are added to the Rh(I) and Pt(0) *via* oxidative addition, and the substrate is coordinated to the metal center, to promote further insertion and consequent boryl migration to the *β* position (Scheme 1.42). From that point, two possible pathways could complete the catalytic cycle, depending on the nature of the substrate: direct reductive elimination to give the 3,4-diborated product, or tautomerization followed by the reductive elimination to give the 1,4-diborated product (Scheme 1.42). Recently, this proposal has been corroborated with DFT calculation by Marder and coworkers. [102]



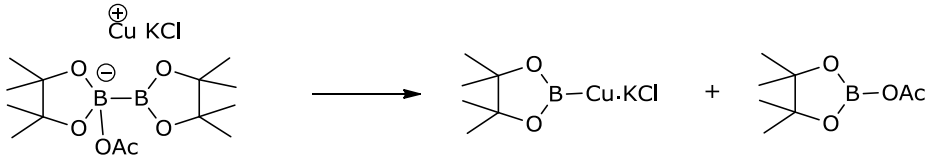
Scheme 1.42 Catalytic cycle of β-boration reaction.

1.3.3 Activation of diboron reagent by σ–bond metathesis

The diboron reagent can be also activated via σ–bond metathesis between the diboron reagent and the M-X unit (X = anionic ligand, alkoxide preferentially) without changing the formal oxidation state of the metal.

Considering this type of activation of diboron reagents, the most important transition metals are: copper and nickel.

Miyaura and co-workers [103] used CuCl as precursor and KOAc as additive and they were able to follow the base assisted σ–bond metathesis between the CuCl and B_2pin_2 by ^{1}H-NMR (Scheme 1.43). They reported the first copper catalyzed β–boration of α,β–unsaturated ketones and esters and obtained the corresponding β–borated product after the aqueous work-up.



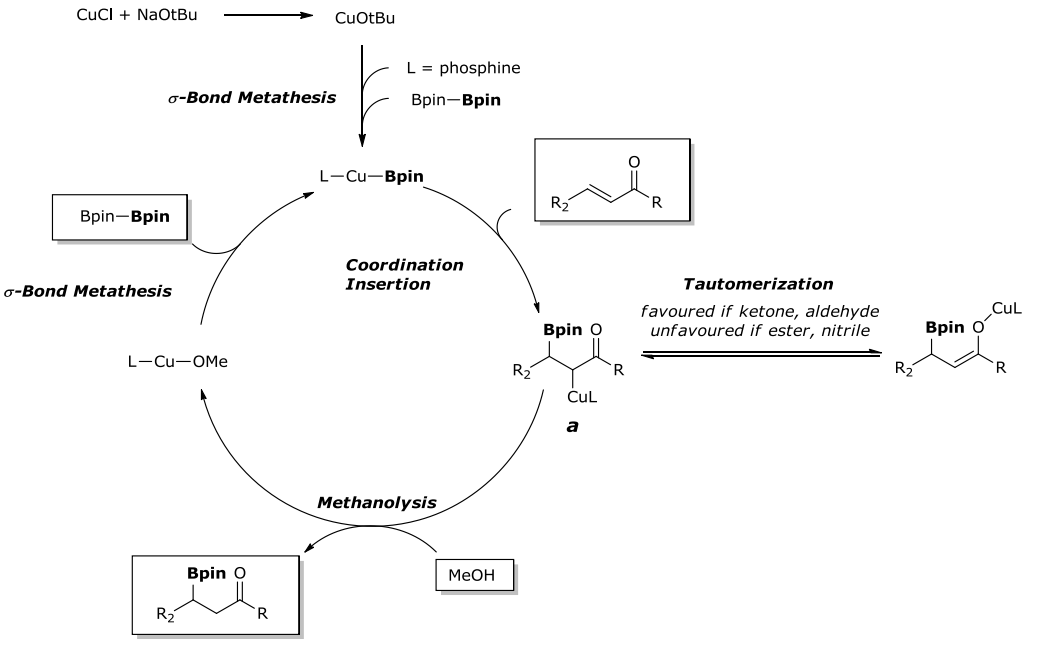
Scheme 1.43 Base assisted transmetallation between B_2pin_2 and CuCl.

At the same time, but independently, Hosomi and co-workers [104] observed the same reaction using CuOTf as precursor modified with the strong basic PBu_3 phosphine.

Both systems required long reaction times in order to obtain good yields. Yun and co-workers in 2006 optimized the reaction with the addition of MeOH to facilitate the recovery of the catalytic species and provide the proton source for the complete formation of the final desired β–borated product with only six hours of reaction. [105] Remarkably, the use of other alcohols in order to accelerate the reaction was also successful. The final catalytic system was formulated as CuCl and phosphine ligand, B_2pin_2 as diboron reagent and a catalytic amount of base and methanol as additive.

The postulated mechanism involved the CuOR formation and further via σ–bond metathesis with B_2pin_2 to give the catalytically active Cu-Bpin species (Scheme 1.46).

The boryl-copper species interacts with the substrate as a Michael addition providing an organoboron copper intermediate which can be tautomerizated to form the corresponding copper-enolate. Methanolysis of both species provide the β-borated product and copper(I)-methoxide, which interacts with B_2pin_2 to regenerate the catalytically active species (Scheme 1.44).



Scheme 1.44 Postulated catalytic cycle of the Cu-catalyzed β-boration reaction of α,β-unsaturated olefins.

A more detailed mechanism was suggested by Lin, Marder and coworkers based on density functional theory calculations. [106] They have shown that both acrolein and methylacrylate, an α,β-unsaturated aldehyde and an 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, [107] while in the case of the ester the tautomerization did not occur due to the inertness of the ester group.

The successful development of an asymmetric variant of the copper mediated β–boration of acyclic α,β–unsaturated carbonyl compounds was first described by Yun and coworkers after they had screened a variety of chiral bidentate phosphine ligands. [108] In particular, the use of the planar chiral ligands (*R*)-(*S*)-josiphos and

(*R*)-(*S*)-NMe_2-PPh_2-Mandyphos provided the β–borated products in more than >90% enantiomeric excesses.

Shibasaki *et al.* [109] and Yun *et al.* [110] developed the first approach to the enantioselective β–boration of cyclic α,β–unsaturated ketones. Yun and coworkers discovered that (*R*,*S*)-Taniaphos induced the highest asymmetric induction for a series of cyclic enones. Shibasaki and co-workers found that the chiral diphosphine QuinoxP* was also an excellent chiral ligand for the cyclic β–substituted α,β–unsaturated ketones. Moreover, Shibasaki and coworkers performed the reaction without protic additives to provide new transformations from the corresponding boron enolates with electrophiles such as benzaldehyde for aldol reaction and acid hydrolysis.

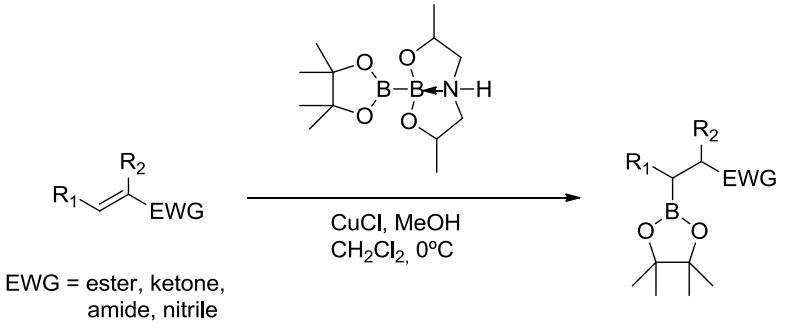
Asymmetric induction could also be achieved using chiral N-heterocyclic carbene ligands (NHC). Our group in collaboration with Pérez modified Cu(I) complexes with chiral NHC ligands and used them in the β–boration of α–methyl substituted esters inducing a variable degree of enantioselection for the first time for these substrates. [111] The benefits provided by this system led our group to perform an enantioselective β–boration of α,β–unsaturated aldehydes, which are considered to be the most challenging α,β–unsaturated carbonyl compounds. Hong and coworkers [112] used isoquinoline-based diaminocarbenes in copper-catalyzed β–boration of α,β–unsaturated amides to obtain enantiomeric excesses up to 86%. Similarly, Hoveyda's group has used Cu(I)-NHC complexes as catalysts in the enantioselective conjugate addition of B_2pin_2 to acyclic β–disubstituted α,β-unsaturated carboxylic esters, ketones and akylthioesters. [113]

Recently, Sawamura and coworkers demonstrated the enantioselective conjugate addition of alkylboranes to imidazole-2-yl α,β–unsaturated ketones catalyzed by a copper(I)-chiral heterocyclic carbene (NHC) complexes. [114]

Another new approach has been developed by Song and coworkers: an efficient copper(I)-catalyzed asymmetric boron conjugate addition using a new bicyclic

triazolium ligand with mixed planar and central chirality. [115] This protocol was highly efficient and gave a variety of chiral secondary alkylboronates in 97-99% *e.e.* values.

During the last years, much effort has been devoted to discover new conditions to promote the catalytic β–boration reducing the presence of base or additives. In that context, Santos and coworkers reported that the base can be eliminated from the catalytic system if the diboron reagent is intramolecularly activated. [116] They prepared a mixed sp^2-sp^3 diboron reagent to β–borate a number of α,β–unsaturated compounds using CuCl as a catalyst and MeOH as the only additive (Scheme 1.45).



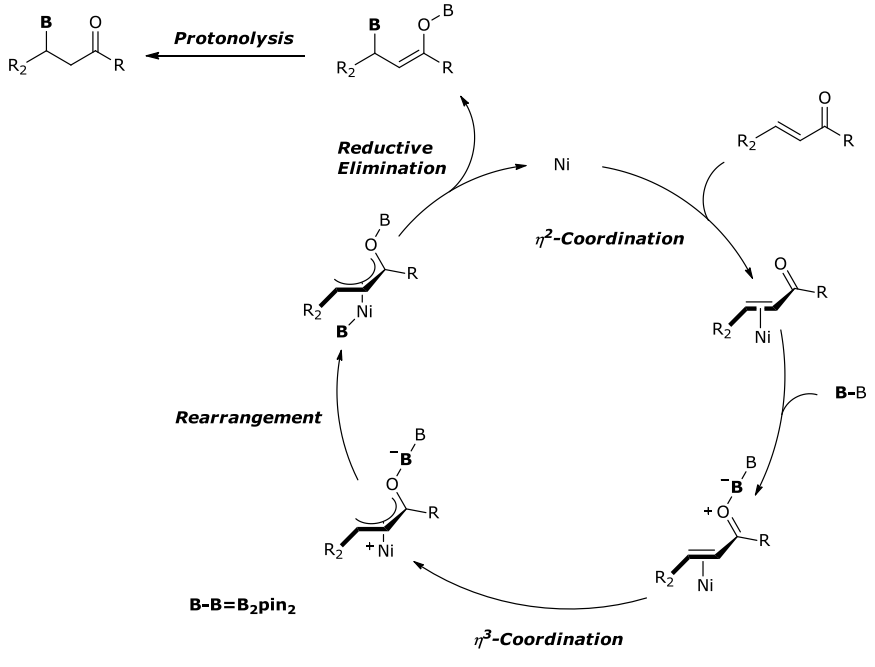
Scheme 1.45 A mixed diboron reagent applied to the copper-catalyzed β–boration reaction.

Most recently, they discovered that the use of amines could promote the β–boylation of α,β–unsaturated carbonyls using Cu(II) systems. [117] Remarkably, the reactions were carried out in water and open to air.

Shortly after, Kitanosono and coworkers reported the first copper(II)-catalyzed enantioselective boron conjugate addition in water using $Cu(OH)_2$ and chiral bipyridine ligands. [118]

Oshima and coworkers have found that Ni(0) complexes also catalyzed the β-boration of α,β-unsaturated carbonyl compounds. [119] The system, similar to the Cu(I) catalysts, required the addition of base and alcohol. The authors have

proposed a reaction mechanism whereby, as the first step, the substrate coordinated to the Ni(0) precursor via the C=C double bond. After the formation of the η^2-nickel complex, the coordinated substrate activated the diboron reagent via a Lewis acid-base interaction between the carbonyl functional group and the empty *p*-orbital of one of the boron atoms (Scheme 1.46).



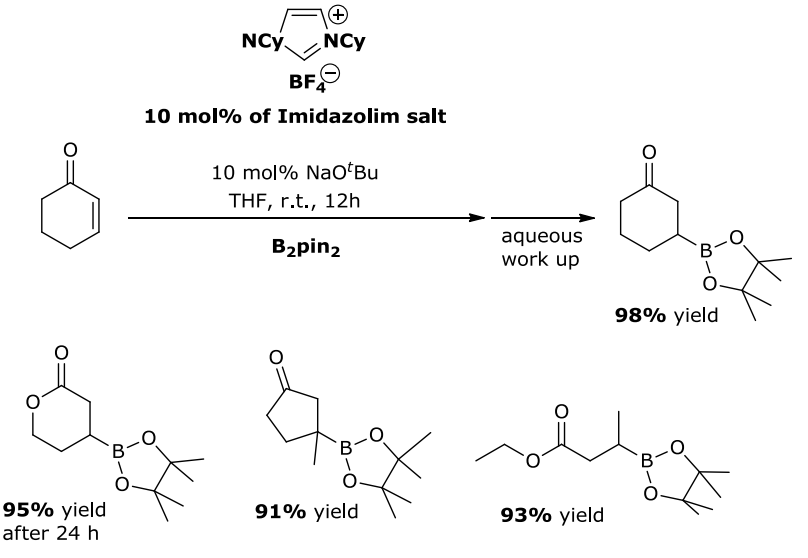
Scheme 1.46 Postulated catalytic cycle of β-boration of α,β-unsaturated carbonyl compounds with Ni complexes.

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

1.3.4 Organocatalytic approaches

The activation of diboron reagents had generally been attributed to a direct interaction between the reagent and transition metal complexes, until Miyaura and co-workers observed that AcO^-activated diborons by Lewis acid–base interactions. [103b] The formed [$B_2pin_2 \cdot AcO^-$] adduct (Scheme 1.45) facilitated the heterolytic cleavage of the B–B bond and the transference of one boryl moiety to the copper(I) center.

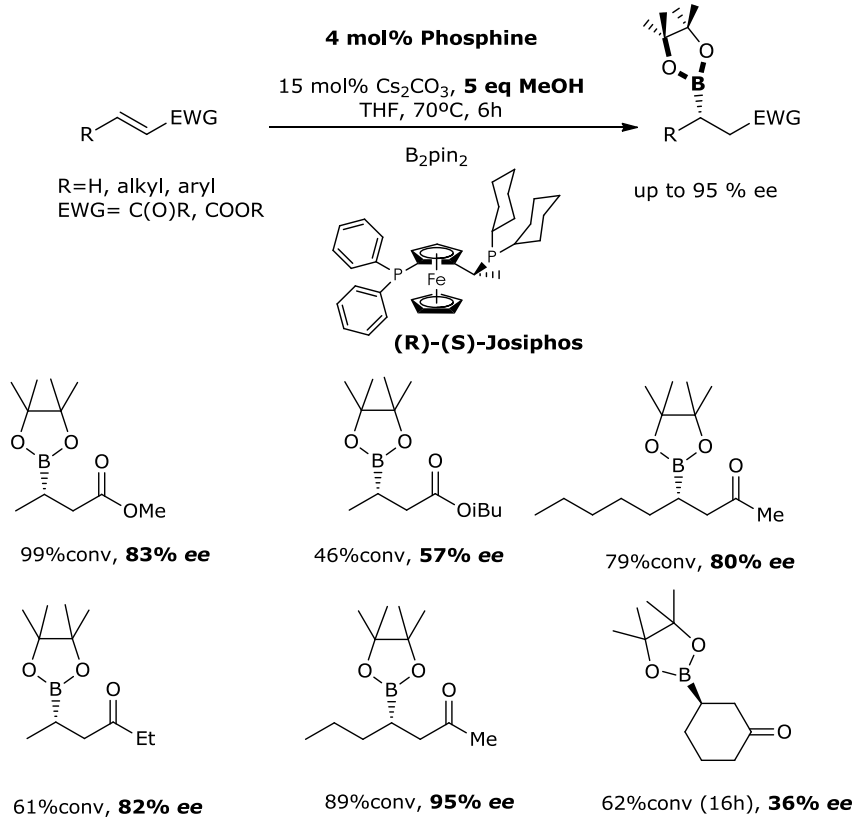
It was not until 2009 when Hoveyda and co-workers reported the first metal free system to activate tetraalkoxydiborons towards the efficient C-B bond formation using 10 mol% of an imidazolium salt and equimolar amount of sodium *tert*-butoxide as catalyst (Scheme 1.49). [120] The authors postulated that the *in situ* generated nucleophilic N-heterocyclic carbene could interact with B_2pin_2 to activate it. Under these reaction conditions (Scheme 1.47), cyclic and acyclic α,β-unsaturated ketones or esters were quantitatively β-borated.



Scheme 1.47 Metal free β-boration reaction reported by Hoveyda and coworkers.

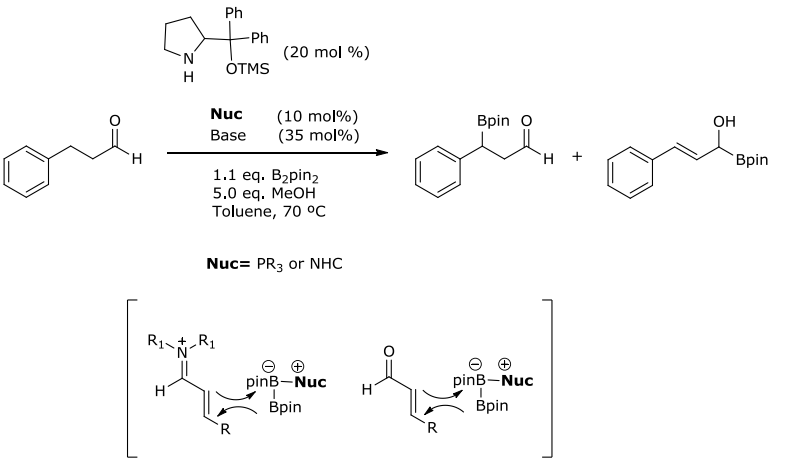
Independently from Hoveyda's discovery, some members of our group developed the first asymmetric organocatalytic β-boration reaction based on the use of

Brönsted base, methanol and chiral phosphines in the presence of B_2pin_2. [121] Using the adequate base and phosphine, high conversions and high levels of enantiomeric excess (*ee*) could be obtained with a wide range of α,β-unsaturated carbonyl compounds (Scheme 1.48).



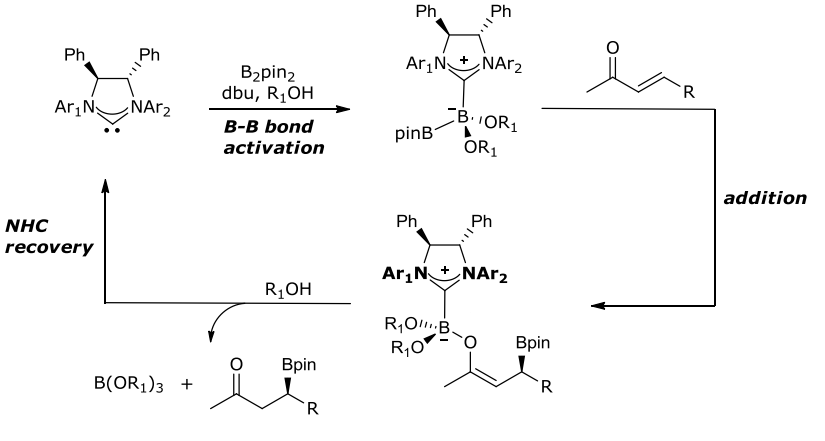
Scheme 1.48 General scheme of the reaction conditions for the first asymmetric metal-free β-boration reaction.

Later on, Córdova and coworkers [122] reported the organocatalytic β-boration of aldehydes facilitated by the *in situ* iminium formation (Scheme 1.49).



Scheme 1.49 Organocatalytic β-boration by means of iminium intermediates.

More recently, Hoveyda and coworkers have reported the asymmetric version of the organocatalytic β-boration with chiral NHC-s. [123] Towards this end the authors used, 7.5 mol% imidazolium salt, 30 mol% dbu (1,8-diazabicyclo[5.4.0]undec-7-ene.) and 60 eq. of MeOH to perform the β-boration of a series of α,β-unsaturated carbonyl compounds obtaining relatively high levels of enantioinduction within a temperature range about 22ºC- 50ºC. Although MeOH was crucial for an active system, the authors suggested that the NHC activates the diboron reagent through a Lewis acid-base adduct (Scheme 1.50).

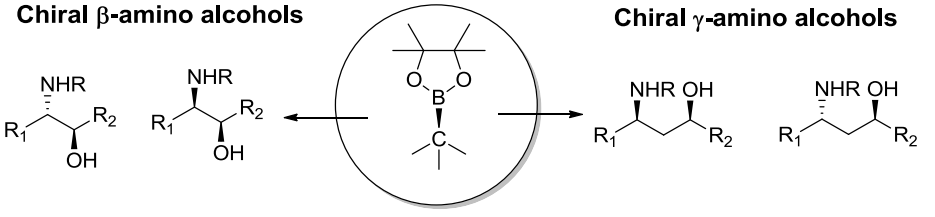


Scheme 1.50 Mechanistic proposal for the NHC mediated enantioselective organocatalytic β-boration reaction.

The activation of diboron reagents by organocatalysis is the latest development in the area of catalytic boron addition reactions and more investigation is needed to understand the mechanism. In this context, our group has investigated the role of the phosphine, methanol and base in the organocatalytic β–boration reaction. [124] The results have demonstrated that under appropriate conditions the Brönsted base is not necessarily requiered to activate the diboron reagent. Instead, the phosphine becomes essential, since it attacks the electrophilic substrate resulting in the formation of zwitterionic phoshonium enolate. This specie can further deprotonate MeOH when B_2pin_2 is present forming eventually the ion par $[\alpha\text{-}(H),\beta\text{-}(PR_3)\text{-ketone}]^+\text{-}[B_2pin_2\cdot MeO]^-$ which is responsible for the catalytic reaction.

1.4 Objectives and proposals

This thesis focuses mainly on developing a new general methodology to prepare γ- and β-amino alochols using organoboranes as intermediates (Scheme 1.51).



Scheme 1.51 New synthetic routes to synthesize amino alcohols using organoboron compounds.

Simultaneously, the inherent concept of diastereoselection and enantioselection becames part of our deep study.

The objectives of this study are summarized in the following points:

- ✓ Asymmetric copper or iron catalyzed β–boration of α,β–unsaturated carbonyl compounds.
- ✓ Stereoselective reductions of β–boryl imine or carbonyl compounds.
- ✓ Developing one-pot method to synthesize γ–amino alcohols with high control of the enantio- and diastereoselectivity.
- ✓ Developing new organocatalytic approaches to synthesize γ-amino alcohols.
- ✓ Asymmetric metal free addition of pinacolboryl moieties to tosylaldimines to synthesize chiral β–amino alcohols.

1.5 References

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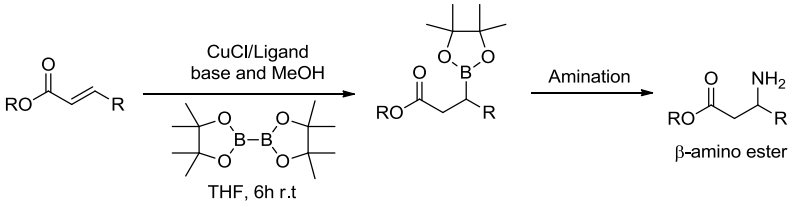
Chapter 2: Synthesis of enantioenriched β–boryl imines

Table of contents

2.1 Preliminars

Our initial attempts to develop efficient synthetic routes towards γ–amino alcohols were inspired by the work of Yun and coworkers, [1] who efficiently β–borated α,β–unsaturated esters with bis(pinacolato)diboron (B_2pin_2), and copper(I)-diphosphine complexes as catalysts.

We were interested in the β–boration of α,β-carbonyl compounds followed by conversion of the C-B bond into C-N bond to obtain β–amino ketones or esters as precursor of the γ–amino alcohol (Scheme 2.1).



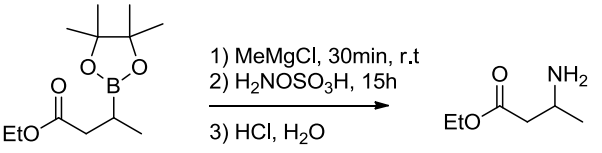
Scheme 2.1 Hypothetical synthetic scheme to obtain β–amino esters.

The β–boration was first undertaken using (*E*)-ethyl crotonate as substrate, copper (I) chloride as catalyst precursor, triphenylphosphine as ligand, bis(pinacolato)diboron as reagent (1.1 eq.), NaO*t*Bu as base (9 mol%), MeOH as protic additive (2 eq.), and THF as solvent (2 mL). The reaction was carried out at room temperature, and after six hours of reaction time, the conversion was completed (99%). The β–boryl ester was purified by flash chromatography.

.

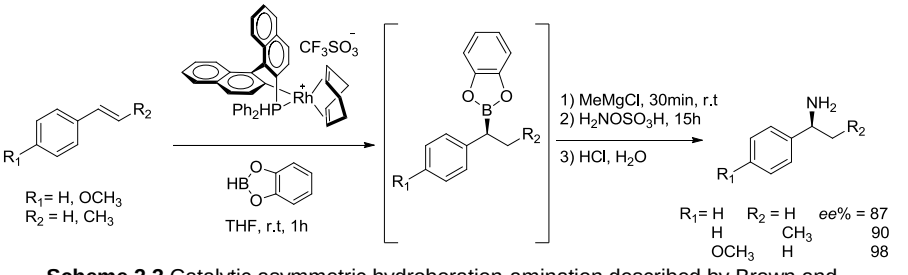
To the best of our knowledge, three different reported strategies described the conversion of the B-C bond into the B-N bond:

1) The common methods and reagents for electrophilic amination do not affect boronic acids and their esters. For this reason, firstly the boronic ester has to be transformed into a trialkylborane with Grignard reagents. The resulting borane would be sufficiently electrophilic to react at room temperature with the aminating reagent, hydroxylamine-O-sulfonic acid, to form the β–amino ester (Scheme 2.2). [2]



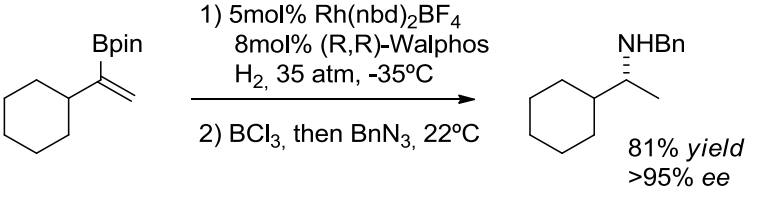
Scheme 2.2. Hypothetical synthetic scheme to convert B-C bond into B-N bond.

Using this strategy, Brown and coworkers successfully synthesized primary amines from vinylarenes *via* catalytic asymmetric hydroboration-amination sequence [3] with total retention of the configuration (Scheme 2.3).



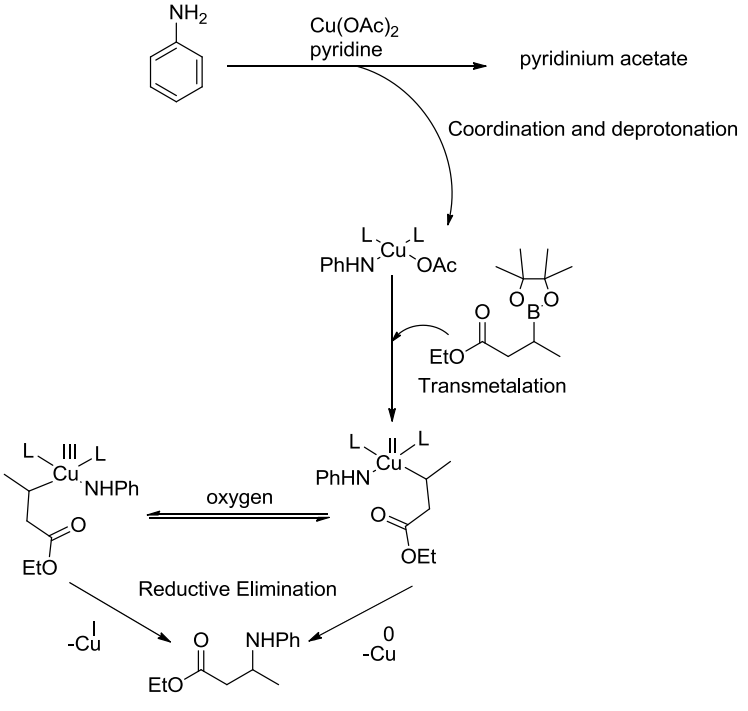
Scheme 2.3 Catalytic asymmetric hydroboration-amination described by Brown and coworkers.

2) Morken and coworkers have described that the C*-Bpin bond can be transformed into C*-NHBn bond using BnN_3 as the aminating reagent (Scheme 2.4). [4] The reaction proceeded with complete retention of the enantioselectivity.



Scheme 2.4 Rh-catalyzed enatioselective hydrogenation of vinyl boronates followed by amination.

3) Finally, the last strategy that we considered was the Chan-Lam coupling. This reaction allows aryl carbon-heteroatom bond formation *via* an oxidative coupling of arylboronic acids. It is initiated in the presence of base by a stoichiometric amount of copper(II) salt, often acetate, or a catalytic amount of copper catalyst which is reoxidized by atmospheric oxygen (Scheme 2.5). [5]

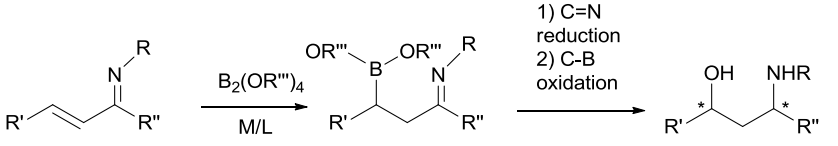


Scheme 2.5 Mechanism of the Chan-Lam coupling.

All three strategies were tested, however, none of them proved to be successful. The two first strategies were too aggressive and resulted in the decomposition of the ester functionality before the boron functional group could have reacted. In the case of the last one, no reaction took place and we could only observe the intact starting material by ^{1}H NMR spectroscopic analysis.

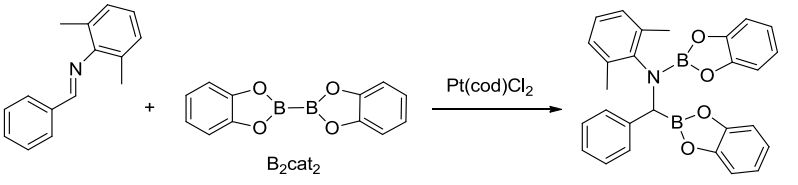
Despite these difficulties, we didn't abandon the main objective and we decided to change the synthetic strategy. We considered the catalytic β–boration of α,β–

unsaturated imines followed by reduction of the imino group and oxidation of C-B bond as an alternative possibility to obtain γ–amino alcohols (Scheme 2.6).



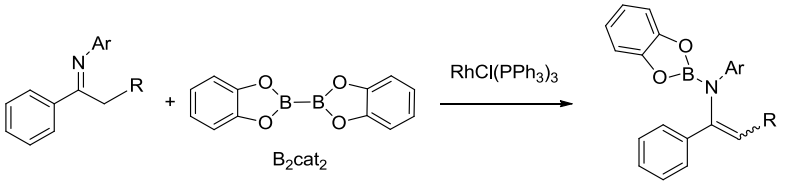
Scheme 2.6 Catalytic β–boration of α,β–unsaturated imines followed by reduction/oxidation.

When we started our study, there were no previous examples on catalytic β–boration of α,β–unsaturated imines. However, the successful boron addition to imines and allylimines demonstrated that transition metals can be used to catalyze the diboration and hydroboration, respectively. For instance, Baker and coworkers [6] efficiently added bis(catecholato)diboron (B_2cat_2) to aldimines in the presence of $Pt(cod)Cl_2$, providing the first direct route to α-aminoboronate esters (Scheme 2.7).



Scheme 2.7 Addition of bis(catecholato)diboron to aldimines using $Pt(cod)Cl_2$.

Alternatively, Westcott and coworkers used rhodium complexes to mediate the diboration of ketimines, where N-borylenamines were obtained as major products (Scheme 2.8). [7]

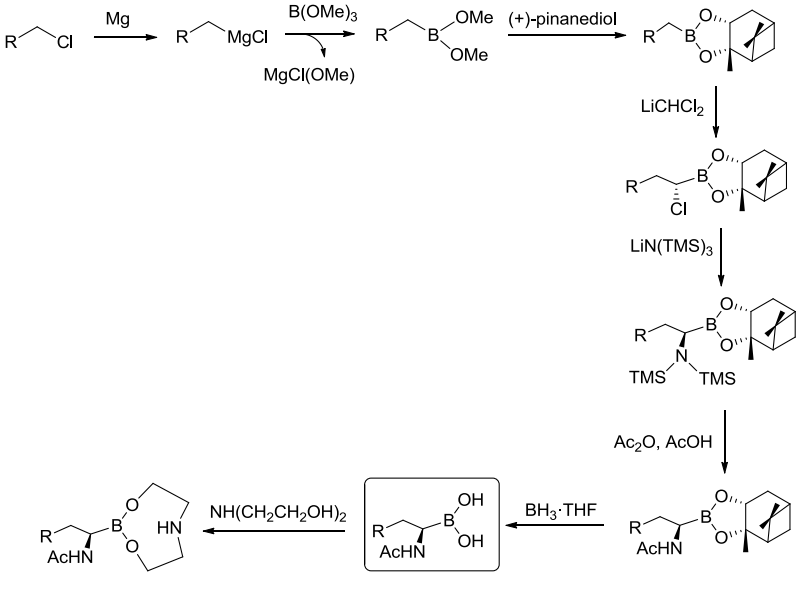


Scheme 2.8 Boron–addition of bis(catecholato)diboron to ketimines using $RhCl(PPh_3)_3$.

Baker and Westcott have also successfully accomplished the hydroboration of enamines, imines and allylimines. [8] It is particularly interesting to note that Rh,

Cu, Ag and Au mediated the addition of catecholborane (HBcat) to C=N, positioning the B atom to the more reactive imine functionality (N) to give aminoboranes.

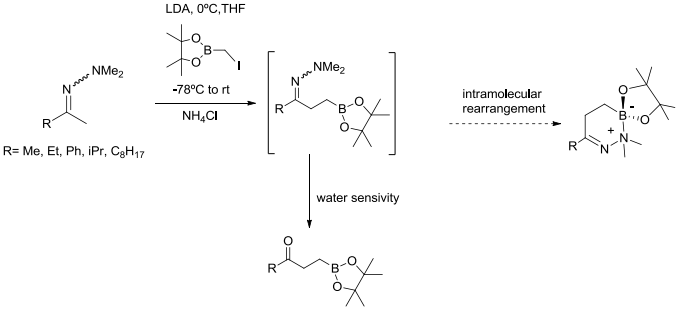
To the best of our knowledge, only two works have been published related to the synthesis of α–aminoboronate esters without the application of transition metals as catalysts. Mattenson and coworkers synthesized enantiomerically pure α-boryl acetamides from chiral boronate esters through homologation reaction, followed by lithium hexamethyldisilazane treatment, which proceeded with complete inversion of the configuration (Scheme 2.9). [9]



Scheme 2.9 Synthetic pathway to obtain enantiomeric 1-acetamido boronic acid designed by Matteson.

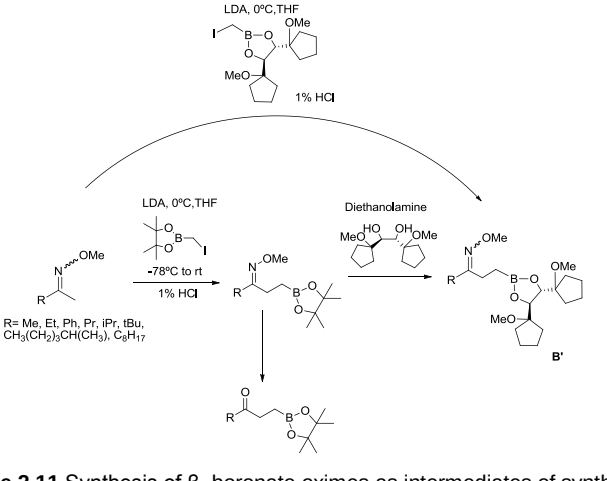
Whiting and coworkers [10] designed a synthetic strategy focused on the preparation of β–amino acid and γ–amino alcohols *via* organoboron compounds as intermediates. They prepared a series of β-hydrazono, oximino methyl ether and imino boronates via the alkylation of an enolate with an α-haloboronate ester for further application in directed asymmetric reduction of the C=N bond by means of a remote chiral boronate ester group. The hydrazone systems showed a

marked hydrolytic sensitivity, probably due to the intramolecular implication of the boronate moiety forming Lewis acid-base interaction with the hydrazine functionality (Scheme 2.10).



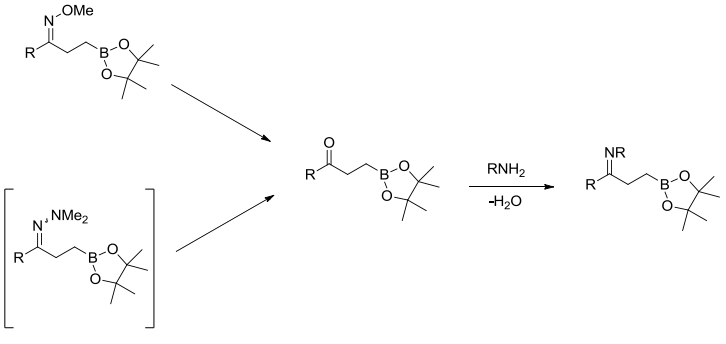
Scheme 2.10. Preparation of hydrazone systems that showed hydrolytic sensitivity.

However a series of β-boronate oxime ethers could be efficiently synthesized preferentially as the *E* stereoisomer (except for R = Me, Et) (Scheme 2.11). From that range of stable, achiral pinacol-based β-boronate O-methyloximes, subsequent routes allowed the preparation of the analogue chiral β-boronate oxime ether products (**B'**) using the transesterification protocols with chiral diols (Scheme 2.10). However, the same product could also be prepared by the deprotonation-alkylation sequence with the corresponding chiral iodomethyl boronate.



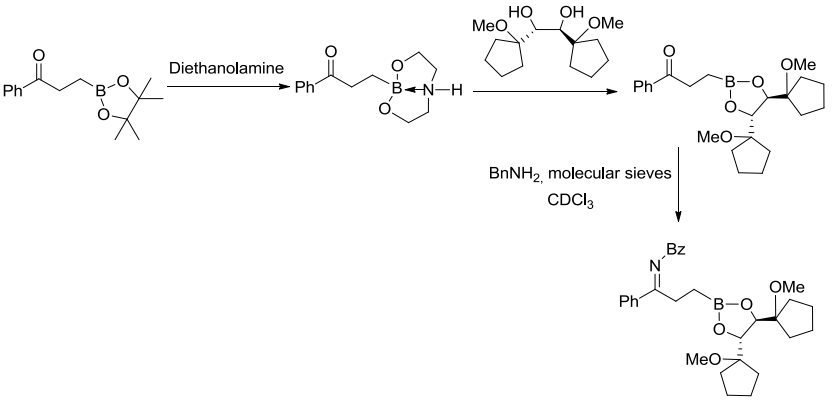
Scheme 2.11 Synthesis of β–boronate oximes as intermediates of synthesis.

Neither the chiral or achiral β-oximo methyl ether boronate showed evidence of boron intramolecular chelation with the nitrogen or oxygen atoms. Despite their evident stability, the hydrolysis of the oxime ether derivatives could provide the corresponding β-keto boronates which could be used as the starting material for β-imino boronate synthesis. Alternatively, the hydrolytically unstable β-hydrazone boronate also provided the β-keto boronate products, which form the desired β-imino boronate derivative through condensation with primary amine (Scheme 2.12).



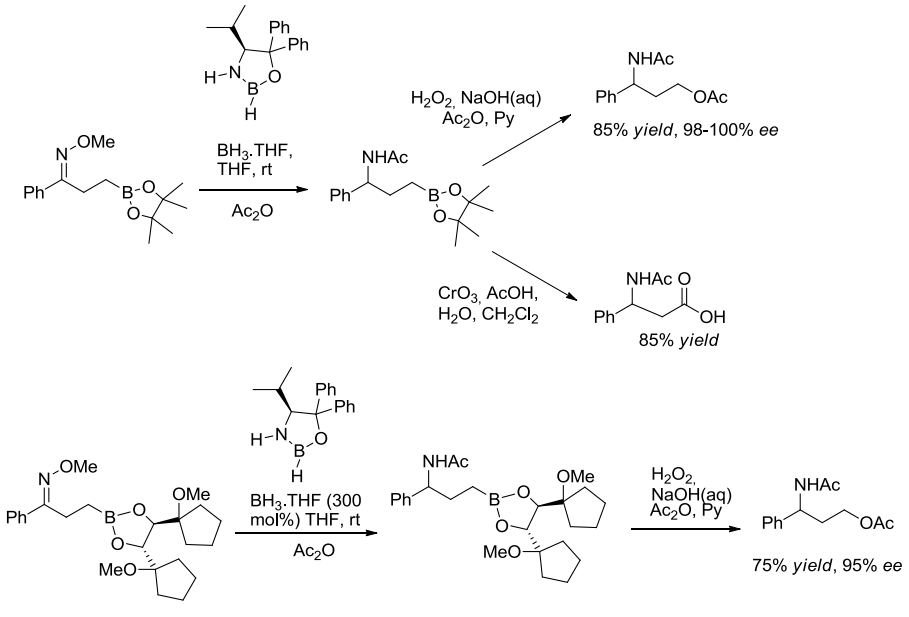
Scheme 2.12 Formation of β–keto boronate through hydrolysis of β–oximo methyl ether or β–hydrazone boronate. Subsequently, the formation of β–imino boronate derivatives is possible *via* condensation with primary amines.

The chiral β-imino boronate compounds, could be efficiently prepared from the β-keto boronates, through transesterification with diethanolamine followed by the replacement of the diethanolamine with a chiral diol (Scheme 2.13). Further conversion into the corresponding chiral imine (R = alkyl or aryl) in the presence of molecular sieves, as catalyst and dehydrating reagents, provided the desired product as a mixture of diastereoisomers containing the thermodynamically favoured *E*-isomer as the major component.



Scheme 2.13 Synthesis of chiral β–imino boronate compounds.

The efficient synthesis of a series of β-hydrazono, oximino methyl ether and imino chiral boronate esters allowed Whiting and coworkers [11] to study the ability of the chiral boronate function to control the asymmetric reduction of the remote C=N double bond. The reduction of oxime ethers was followed by oxidative cleavage of the boronate ester functionality, providing new routes towards β-amino acids and γ-amino alcohols. It is important to note, however, that the remote homochiral boronate ester did not directly control the asymmetric induction of the oxime ether functionality with the achiral reducing agent, BH_3·THF. Instead, the use of a homochiral reducing agent induced the double-diastereoisomeric effect when a chiral boryl moiety is involved. Therefore, when an oxazaborolidine reagent was added to β-oximino methyl ethers, interesting difunctional products were isolated in high yields and enantiomeric excess values (Scheme 2.14).



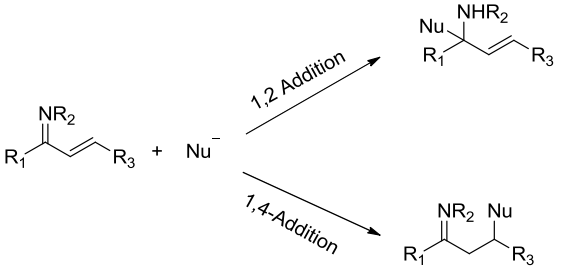
Scheme 2.14 New routes towards β–amino acids and γ–amino alcohols.

With this information in mind, we were interested in developing new routes to prepare γ–amino alcohols, along the unexplored β–boration of α,β–unsaturated imines and determining the influence of the substituents in the imino group.

2.2 Synthesis of α,β–unsaturated imines

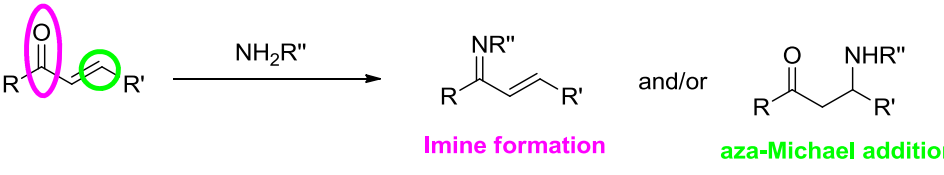
Non-functionalized ketones and aldehydes readily react with primary amines to afford the corresponding imines. [12] The equilibrium can be shifted towards imine formation using dehydrating agents, or by azeotropic distillation or crystallization of the imine from the reaction mixture.

However, α,β-unsaturated imines, also called 1-azadienes, are different from the conventional family of imines due to their ambident electrophilic character. They can etiher undergo 1,2 [13] or 1,4 [14] conjugate nucleophilic addition processes and for this reason the control on the regioselectivity of the addition process is difficult (Scheme 2.15).



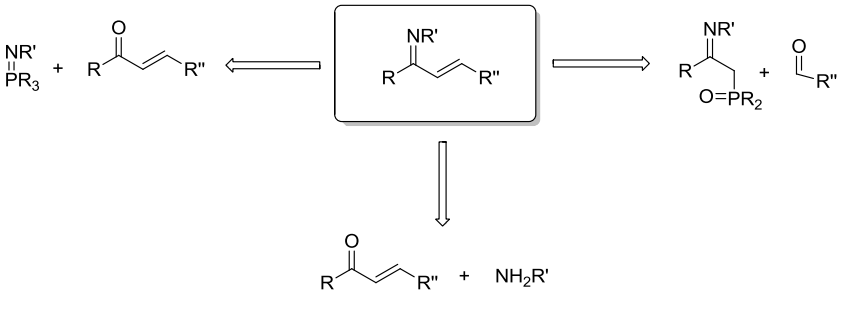
Scheme 2.15 Plausible 1,2 or 1,4 nucleophilic addition to α,β–unsaturated imines.

In addition this double reactivity is a drawback for their synthesis: the condensation of α,β–unsaturated carbonyl compounds with primary amines to obtain the corresponding α,β–unsaturated imines competes against the aza-Michael addition reaction (Scheme 2.16).



Scheme 2.16 Competitive imine formation and aza-Michael addition to α,β–unsaturated ketones.

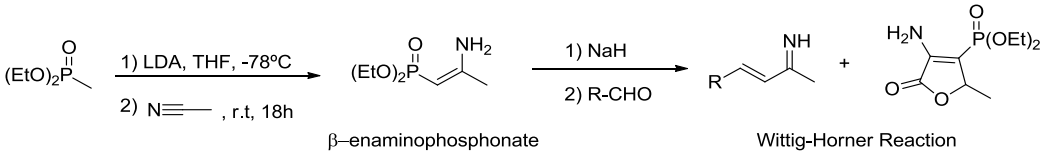
Retrosynthetically, we envisaged obtaining unsaturated imines through three different methods (Scheme 2.17).



Scheme 2.17 Retrosynthetic analysis towards the formation of α,β–unsaturated imines.

For the first method, we planned the synthesis of β–enaminophosphonate using diethyl methylphosphonate and acetonitrile followed by the olefination reaction (Wittig-Horner or Wadsworth-Emmons reaction) with carbonyl compounds to form

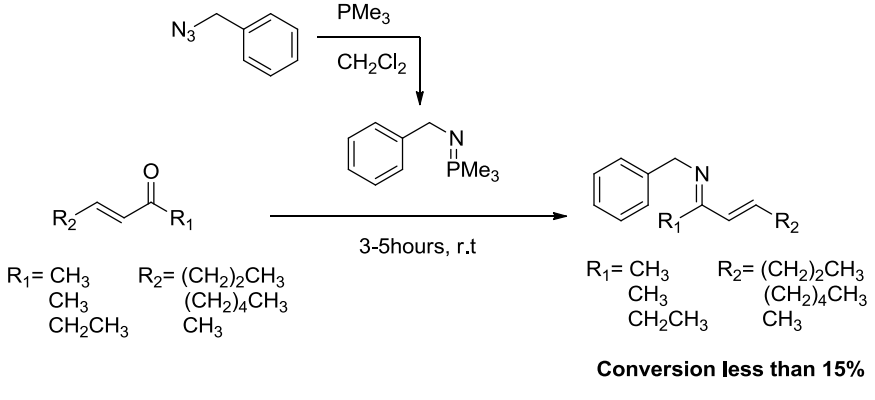
the carbon-carbon (C=C) double bond of the desired α,β–unsaturated imine [15a] (Scheme 2.18).



Scheme 2.18 Synthesis of β–enaminophosphonate followed by the Wittig-Horner reaction to obtain α,β–unsaturated imines.

Unfortunately, we could not obtain the β–enaminophosphonate even using different type of nitriles (acetronitrile, propionitrile and 4-(chlorophenyl)acetonitrile).

The second synthetic strategy was inspired by Aparicio and coworker's work [15b]. They developed an efficient synthesis of α,β–unsaturated imines derived from α–aminoesters through an aza-Wittig reaction of phosphazenes with β,γ-unsaturated α–ketoesters. We followed the same experimental procedure but alkylic α,β–unsaturated ketones were used as starting material (Scheme 2.19). Unfortunately, less than 15% of conversion was observed in all the cases.



Scheme 2.19 Alternative synthesis of α,β–unsaturated imines through an aza-Wittig reaction.

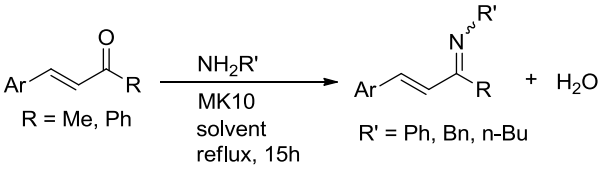
Finally, the last method was based on the condensation reaction of α,β–unsaturated ketones with primary amines or hydroxylamine in the presence of

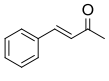
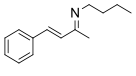
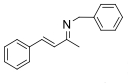
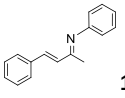
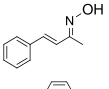
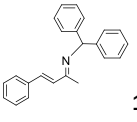
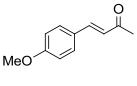
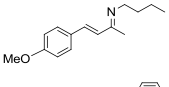
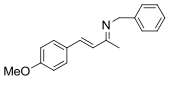
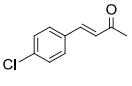
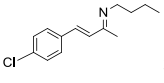
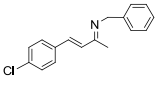
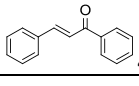
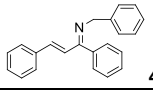
montmorilloite clay (MK10). [16] MK10 is comparable to molecular sieves in terms of dehydrating properties. [17] The yields of the isolated α,β-unsaturated imines **1b**-**f** were high (Table 2.1, entries 1-5) and comparable to the yields obtained in other synthetic procedures described in the literatura. [18] Importantly, we observed different *syn/anti* ratios depending on the N-substituent of the imino group although the *anti* isomer was the major product in all cases, most probably due to steric effects.

We have found that to obtain sufficient chemoselectivity towards the imine formation, an aryl substituent on the β-carbon of the ketones is crucial. In the case of aliphatic ketones as 2-cyclohexen-1-one or *trans*-3-nonen-2-one, the aza-Michael addition dominated independently of the reaction conditions.

The scope of the study involved the synthesis of a series of α,β-unsaturated imines with subtle but consistent variations of electronic properties on the structure. The imines N-(4-(*p*-methoxyphenylbut-3-en-2-ylidene)butane-1-amine (**2b**) and 1-phenyl-N-(4-*p*-methoxyphenylbut-3-en-2-ylidene)methanamine (**2c**) were prepared and isolated in high yields, by the condensation of the corresponding ketones and amines in the presence of MK-10 (Table 2.1, entries 6, 7). Similarly, the imines N-(4-(*p*-chlorophenylbut-3-en-2-ylidene)butan-1-amine (**3b**) and phenyl-N-(4-*p*-chlorophenylbut-3-en-2-ylidene)methanamine (**3c**) were synthesized, however, the isolated yields were only moderate (Table 2.1, entries 8, 9).

Table 2.1. Synthesis of α,β-unsaturated imines from the corresponding α,β–unsaturated ketone and amine [a].



Entry	Ketone	Imine	Isolated Yield %	Ratio *syn/anti*
1	 **1a**	 **1b**	73	1/9
2	"	 **1c**	89	3/7
3	"	 **1d**	78	0/10
4	"	 **1e**	95	1/1
5	"	 **1f**	85	4/6
6[b]	 **2a**	 **2b**	95	2/8
7[b]	"	 **2c**	91	2/8
8[b]	 **3a**	 **3b**	73	2/8
9[b]	"	 **3c**	73	2/8
10[c]	 **4a**	 **4c**	43	2/8

[a] Standard conditions for the imine synthesis: 1 mmol ketone, 1.1 mmol amine, 100 mg MK-10, rt, 15h, solvent: CH_3CN (2.5 mL); [b] solvent: MeOH; [c] solvent: hexane, T= 70ºC.

In order to analyze the influence of bulkier substituents on the imine carbon, the benzylimine **4c** of benzylideneacetophenone was prepared and isolated in 43% yield (Table 2.1, entry 10). Figure 2.1 shows the molecular structure of imine **4c** determined by X-ray crystallography. The C(1)-N(1) distance is 1.285 Å, indicating the double bond character of the imine functionatily. The C(2)-C(3) distance of 1.322 Å and the angle 125.9º confirms the *E*-geometry of the C=C double bond. The co-planarity found for the imine N(1)-C(1), and alkene C(2)-C(3) atoms, and the short distance for a single bond between C(1)-C(2), indicates some degree of conjugation along the N(1)=C(1)-C(2)=C(3) π-electron system.

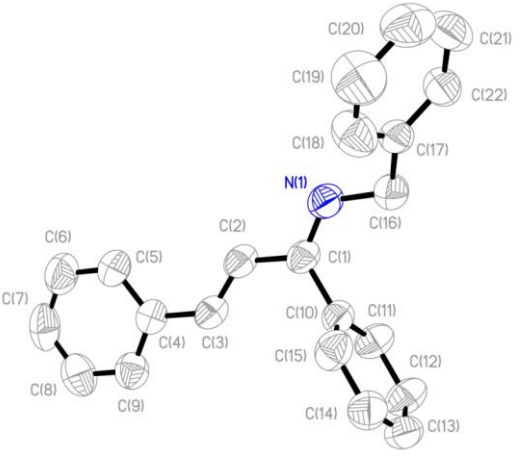


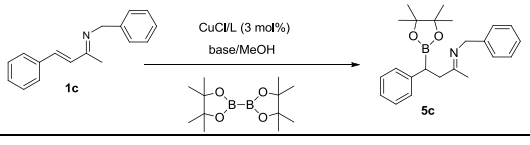
Figure 2.1. Molecular diagram of benzylimine **4c**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (º): C(1)-N(1) 1.285(3), C(1)-C(2) 1.465(3), C(1)-C(10) 1.501(3), N(1)-C(16) 1.462(3), C(2)-C(3) 1.322(3), C(3)-C(4) 1.472(3), N(1)-C(1)-C(2) 117.12(19), N(1)-C(1)-C(10) 124.87(19), C(2)-C(1)-C(10) 118.00(19), C(1)-N(1)-C(16) 119.92(19). C(1)-C(2)-C(3) 125.9(2).

2.3 Copper-catalyzed β–boration of α,β–unsaturated imines

In the absence of catalysts, the addition of one equivalent of bis(pinacolato)diboron (B_2pin_2) or bis(catecholato)diboron (B_2cat_2) to the imine (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine (**1c**) did not lead to the formation of any borylated product at room temperature. Therefore, we sought

potential catalysts for the reaction. The first catalytic systems to mediate the β–boration of α,β–unsaturated carbonyl compounds were based on platinum [6] or rhodium. [7] However, inexpensive metals (Cu or Ni) are currently used for the catalytic β–boration of α,β–unsaturated carbonyl compounds as convenient alternatives of the costly precious metal catalysts. [19] For this reason, we selected catalytic systems based on Cu salts modified with phosphine ligands. B_2pin_2 was selected as the most practical boron reagent considering its reactivity and stability. [20] Imine **1c** and B_2pin_2 did not react in the presence of 3 mol% of CuCl (Table 2.2, entry 1). On the other hand, when CuCl was combined with tricyclohexylphosphine (PCy_3), a moderate conversion into the β–boryl imino derivative was observed after six hours (Table 2.2, entry 2). The activity of the $CuCl/PCy_3$ system did not improve when MeOH was applied as additive, despite the fact that MeOH enhanced the reaction rates in β–boration of α,β–unsaturated carbonyl compounds [21] (Table 2.2, entry 3). However, complementing the previous additive with base (9 mol%) resulted in the quantitative formation of the desired product (Table 2.2, entry 4).

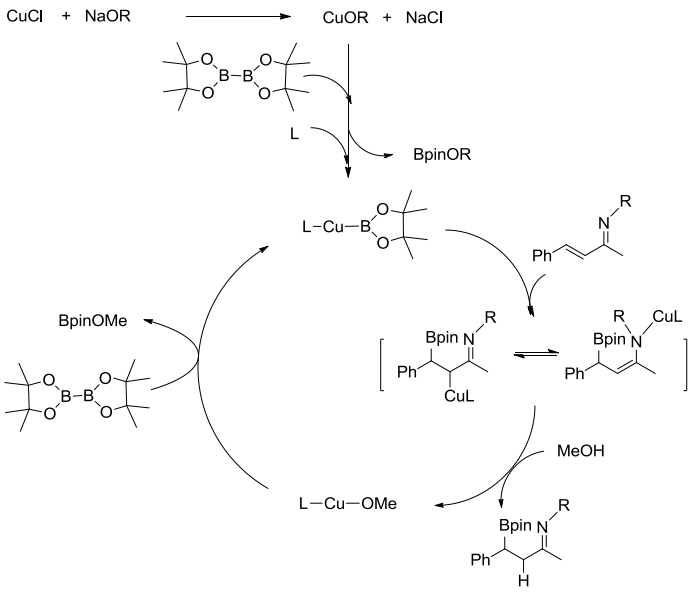
Table 2.2. Cu-mediated catalytic β–boration of α,β–unsaturated imines with bis(pinacolato)diboron (B_2pin_2) [a].



Entry	Imine	Catalytic system	Additive	Base	Conv. (%)[b] [I.Y.%]
1	**1c**	CuCl	---	---	-
2	**1c**	$CuCl/PCy_3$	---	---	32
3	**1c**	$CuCl/PCy_3$	MeOH	---	29
4	**1c**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [82]
5	**1c**	$CuCl/PCy_3$	MeOH	NaOAc	99
6	**1c**	$CuCl/PCy_3$	MeOH	NaOMe	99
7	**1c**	$CuCl/PCy_3$	MeOH	NaOH	99

[a] Standard conditions: Substrate / Cu = 1/0.03. B_2pin_2 = 1.1 eq., NaO*t*Bu = 9 mol%, MeOH = 20 µL Solvent: THF (2.5mL). T = 25ºC, t = 6h. [b] Determined by ^1H NMR spectroscopy.

It seemed that different bases could be applied to reach the total conversion (Table 2.2, entries 4-7). Miyaura and coworkers [22] have previously reported that the key step in the mechanism of the selective β–boron addition of bis(pinacolato)diboron to α,β–unsaturated ketones, esters and nitriles was the transmetallation between the diboron reagent and Cu salts. The base promotes the substitution of Cl^- ligand with alkoxide in the Cu(I) complex, and subsequently assists the σ-metathesis step between the Cu-OR species and the diboron reagent. Shibasaki and coworkers [23] also attributed to LiO*i*Pr the role of an effective generator of an active allylcopper complex from CuF/phosphine and allylboronate. In this context, we have postulated a reaction mechanism based on a catalytic cycle in which the base assists the heterolytic cleavage of the diboron reagent to promote the formation of the copper-boryl intermediate. Michael addition type 3,4-insertion into the Cu-B bond will result in the formation of C_β-B and C_α-Cu bonds. This species migh tautomerize into the corresponding metalloenamine form. Usually, MeOH is added as the H^+ source to accelerate the reaction. [21] However, in our case the MeOH was not crucial, indicating an enchanced reactivity of the metalloenamine (Scheme 2.20). It seems that even traces of moisture in the solvent can act as a proton source. Alternatively, the metalloenamine intermediate might be able to transmetallate directly with the boron reagent, resulting in the formation of the 1,4-diborated intermediate and the regeneration of the catalytically active copper-boryl complex. As discussed above, the 1,4-diborated intermediate readily hydrolyzes, providing the desired β–borated product.



Scheme 2.20 Plausible mechanism for β–boration of α,β–unsaturated imines with B_2pin_2.

In order to gain further insight into the increased reactivity of metalloenamines, we studied the competitive β–boration of the α,β–unsaturated imine **1c** and the corresponding ketone in absence of MeOH. We observed that while imine **1c** was smoothly transformed into the β–borated product, the ketone remained almost unreacted (Figure 2.2).

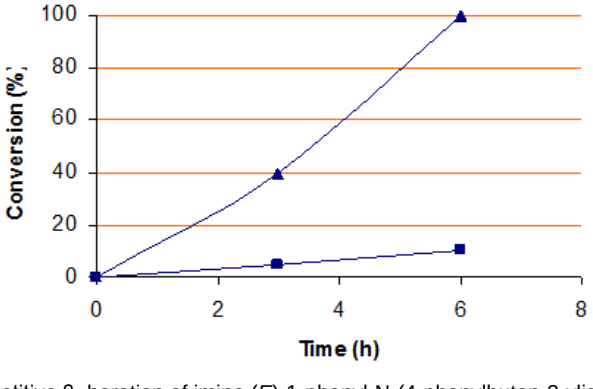
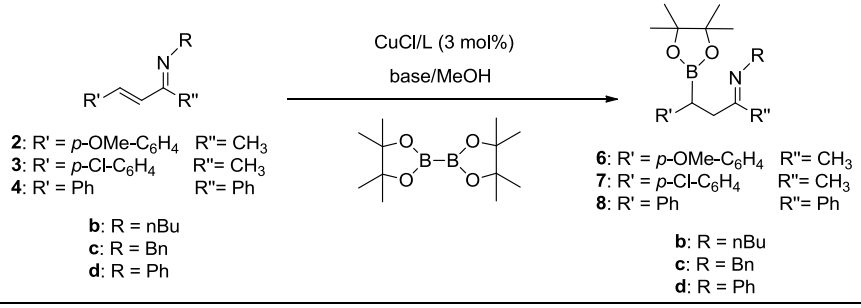


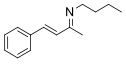
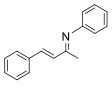
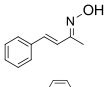
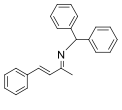
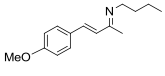
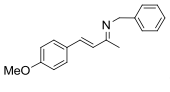
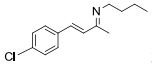
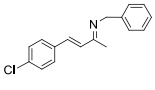
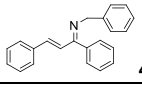
Figure 2.2. Competitive β–boration of imine (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanime **1c** (▲) and *trans*-4-phenyl-3-buten-2-one (■) with B_2pin_2 and in the absence of MeOH.

Under optimized reaction conditions, imines (*E*)-N-((*E*)-4-phenylbut-3-en-2-ylidene)butan-1-amine (**1b**) and (*E*)-N-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**1d**) were also conveniently β-borated, (Table 2.3, entries 1,2). The electronic and steric nature of R in the imino group does not seem to influence the B addition reaction. However, when the imine **1f** and the oxime **1e** were used as substrates, the rate of the β–boration diminished. The imine **1f** needed double the amount of catalyst (6 mol%) to obtain 99% of conversion within the same reaction time (Table 2.3, entry 4), probably due to the steric hindrance.

In the case of the oxime **1e**, only 34% of the substrate was transformed under the standard reactions conditions (Table 2.3, entry 3). Higher catalyst concentration and reaction temperatures did not improve the catalytic performance significantly.
Quantitative conversions were observed for all the other α,β–unsaturated imines (Table 2.3, entries 5-8), except for the β–boration of (*Z*)-N-((*E*)-1,3-diphenylallylidene)-1-phenylmethanamine (**4c**) (Table 2.3, entry 9) which needed longer reaction time to be quantitative, probably due to both the increased steric hindrance around the double bond and the more extended conjugation of the π–electron system.

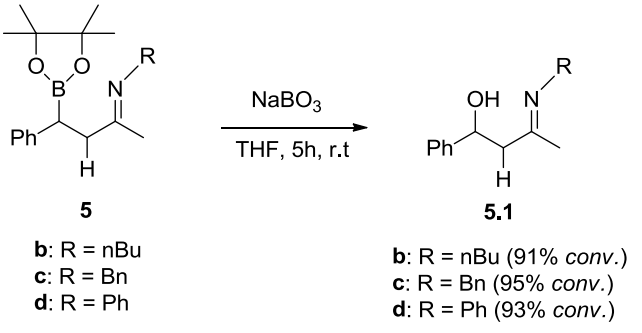
Table 2.3. Cu-mediated catalytic β–boration of α,β–unsaturated imines with bis(pinacolato)diboron (B_2pin_2) [a].



Entry	Imine	Catalytic system	Additive	Base	Conv. (%)[b] [I.Y.%]
1	 **1b**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [70]
2	 **1d**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [40]
3	 **1e**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	34 [29]
4	 **1f**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99[c] [80]
5	 **2b**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [97]
6	 **2c**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [85]
7	 **3b**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [89]
8	 **3c**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99 [85]
9	 **4c**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99[d] [78]

[a] Standard conditions: Substrate / Cu = 1/0.03. B_2pin_2 = 1.1 eq., NaO*t*Bu = 9 mol%, MeOH = 20 µL Solvent: THF (2.5mL). T = 25ºC, t = 6h. [b] Determined by ^1H NMR spectroscopy. [c] 6mo% of Cu/L was used. [d] t =12h.

Eventually, three β-imino boronate intermediates were efficiently oxidized into their β-iminoalcohols in the presence of $NaBO_3$ as oxidizing reagent (Scheme 2.21).



5

b: R = nBu
c: R = Bn
d: R = Ph

5.1

b: R = nBu (91% *conv.*)
c: R = Bn (95% *conv.*)
d: R = Ph (93% *conv.*)

Scheme 2.21 Oxidation of β-imino boronate esters.

We can conclude at this point that β-boryl imines or their analogues β-iminoalcohols can be easily prepared in high yields via a copper-mediated β-boration/oxidation reaction using bis(pinacolato)diboron as the boron reagent.

2.4 Asymmetric copper-catalyzed β–boration: Screening of ligands

Despite the considerable progress in the methodology of stereoselective organic synthesis, optically active amino alcohols still remain attractive and challenging targets. [24] Since these compounds have found important applications as drugs, and as potential chiral ligands in metal-mediated organic reactions, efforts towards their enantioselective synthesis are more than justified.

To the best of our knowledge, β-hydrazono-, oximino methyl ether- and imino-boronates have only been prepared through an enolate alkylation using α-haloboronate esters. [10,11] The reported stable, achiral, pinacol ester β-boronate *O*-methyloximes and hydrazones were examined for subsequent reactions including transesterification protocols with chiral diols for the preparation of the analogue chiral β-boronate oxime ether products and reduction. The

corresponding chiral imino-boronates were too reactive, [11] hence, an alternative and mild synthetic procedure to access β-boronate imine derivatives is much more convenient. In this context, we wondered whether asymmetric copper-catalyzed β–boration could be used to obtain chiral β–boryl imines, which could be conveniently reduced and oxidized towards the desired chiral γ–amino alcohols.

Since there were no examples in the literature of asymmetric β-boration of α,β-unsaturated imines, we decided to use three α,β–unsaturated imines with different imino group (**1b**,**1c** and **1d**) as model substrates, and we focused our efforts on the screening a small but diverse library of potential effective chiral phosphorous ligands (Figure 2.3).

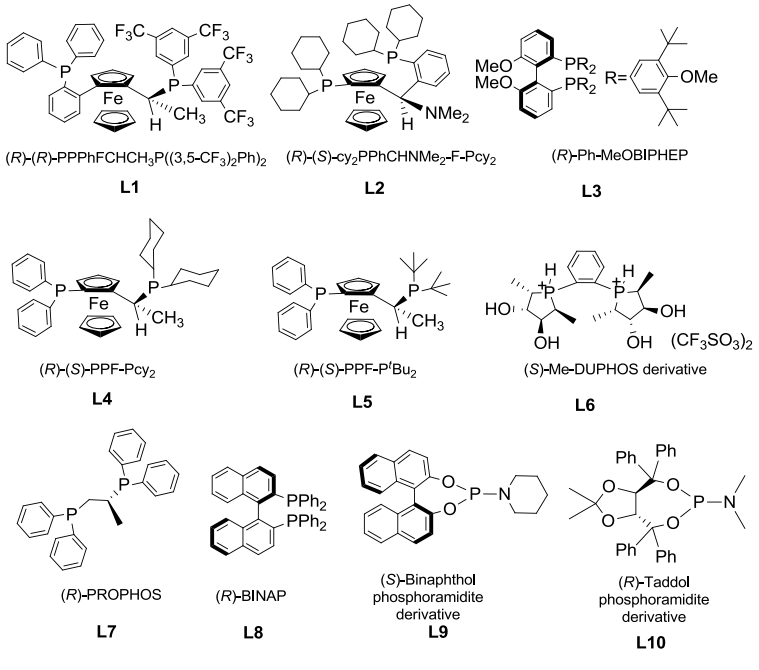


Figure 2.3 Chiral phosphorous ligands applied in copper mediated β-boration of α,β-unsaturated imines.

The β–boration of **1c** with B_2pin_2 was carried out in the presence of 2 mol% of CuOTf (as standard source of Cu salt) modified with 2 mol% of bidentate ligand

(**L1**-**L8**, Figure 2.3) or 4 mol% of monodentate ligand (**L9**, **L10**, Figure 2.3) as catalyst. To guarantee high conversions, 9 mol% of NaO*t*Bu and 2 eq. of MeOH were added. Most of the reactions were completed within 6 hours at room temperature (Table 2.4, entries 1-10).

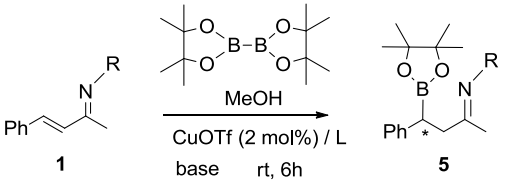
The best result was obtained with Josiphos-type ligand **L4** (Table 2.4, entry 4), which provides complete conversion and, total asymmetric induction (>99% *e.e.*). Taniaphos (**L2**) and Meobiphep (**L3**) were also highly effective for the copper-mediated asymmetric β–boration of **1c** (Table 2.4, entries 2 and 3). The modification of the Cu(I) precursor with the other Josiphos-type ligands **L1** and **L5** resulted in slightly lower stereoselectivities (Table 2.4, entries 1 and 5). Remarkably, the two monodentate chiral phosphoramidite ligands (**L9** and **L10**) gave considerable asymmetric induction, *i.e.* 75% e.e. (Table 2.4, entries 9-10), despite their reportedly poor performance in the analogous β-boration of α,β-unsaturated esters [1]. The lowest activity and enantioselectivity was achieved with the Cu(I)-BINAP (**L8**) catalytic system (Table 2.4, entry 8).

In order to study the influence of the electronic and steric properties of the imino group on this process, we next explored the asymmetric β-boration reaction of (*E*)-*N*-(4-phenylbut-3-en-2-ylidene)aniline (**1d**). Entries 11-20 in Table 2.4 show that the phenyl substituent on the imino group of **1d** notably decreases the reactivity of the substrate in the Cu(I)-mediated catalytic β-boration reaction. The average enantioselectivity also significantly decreases, however we were particularly delighted to see that one of the most accessible chiral ligands, the monodentate phosphoramidite **L9**, promotes the formation of **2b** in quantitative yield and with 95% *e.e.* (Table 2.4, entry 19).

The boration of **1b** could also be carried out with high efficiency. Most ligands provided complete conversions. We only experienced slightly lower activities in the case of Cu(I)/**L1** and Cu(I)/**L8**, which provided 84% and 88% conversions, respectively. Since the enantioselectivies could only be unambiguously

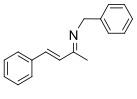
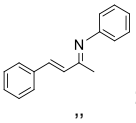
determined from the analysis of the corresponding amino alcohols, these results will be discussed in the following chapters.

Table 2.4. Cu(OTf)/L mediated asymmetric catalytic β-boration of α,β-unsaturated imines **1c** and **1d** with B_2pin_2 [a].



c: R = Bn
d: R = Ph

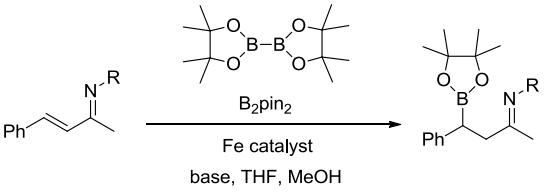
c: R = Bn
d: R = Ph

Entry	Imine	L	Conv.(%)[b]	e.e. (%)[c]
1	 **1c**	**L1**	85	78 (+)
2	''	**L2**	>99	91 (+)
3	''	**L3**	>99	94 (+)
4	''	**L4**	>99	>99 (+)
5	''	**L5**	>99	77 (+)
6	''	**L6**	>99	83 (+)
7	''	**L7**	>99	89 (+)
8	''	**L8**	36	42 (+)
9	''	**L9**	>99	75 (+)
10	''	**L10**	>99	75 (+)
11	 **1d**	**L1**	66	88 (+)
12	''	**L2**	61	63 (+)
13	''	**L3**	79	40 (+)
14	''	**L4**	>99	51 (+)
15	''	**L5**	66	30 (+)
16	''	**L6**	66	30 (-)
17	''	**L7**	67	62 (+)
18	''	**L8**	56	16 (+)
19	''	**L9**	>99	95 (+)
20	''	**L10**	66	66 (+)

[a] Standard conditions: 0.2 mmol substrate, 2 mol% Cu(OTf), 4 mol% monodentate igand, 2 mol% bidentate ligand, B_2pin_2 (1.1 eq), NaO*t*Bu (9 mol%), MeOH (2 eq), THF (1 mL), 25 ºC, 6 h. [b] Conversion calculated by 'H NMR spectroscopy. [c] e.*e.* determined by chiral HPLC analysis.

2.5 Iron assisted organocatalytic β–boration of α,β–unsaturated imines

In the light of current debates surrounding sustainable and green chemistry, iron has now become an attractive alternative to homogenous catalysts based on precious metals, because it is abundant, inexpensive, usually less toxic, and thus, environmentally more acceptable. [25] In the literature there is only one example of iron-mediated C-B bond formation using a 1,4-hydroboration of 1,3-dienes to obtain linear (*E*)-γ-disubstituted allylboranes. [26] Consequently, we became interested in the possible application of iron catalysts in the β–boration of α,β–unsaturated imines emphasizing the role of Fe in the reaction (Scheme 2.22).



Scheme 2.22 β–Boration of 1-azadiene using iron precursors as a catalyst.

Again three α,β–unsaturated imines (**1b**, **1c, 1d**) were chosen as the model substrates to carry out the study. The first reactions were performed using **1c** as substrate, in the presence of $Fe(acac)_2$ and base at 70ºC. After 6h of reaction time the β–borated product was formed with 28% conversion (Table 2.5, entry 1).

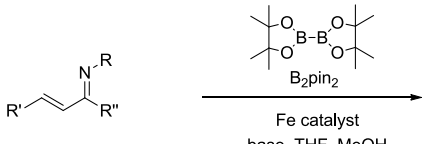
When the reaction was carried out in the presence of 2 mol% of $Fe(acac)_2$ and 4 mol% of PPh_3, the activity increased substantially. We also observed that a pronounced dependence of the activity on the amount of base was present (Table 2.5, entries 2-4). Total conversion was observed when the amount of Cs_2CO_3 was 15 mol%, whereas no product was formed in the absence of base.

The analogous combinations of $FeCl_2/PPh_3$, $Fe(OMe)_2/PPh_3$ and $Fe(acac)_3/PPh_3$ provided less active catalytic systems (Table 2.5, entries 6-8). It is also important to note that in the absence of Fe complex, the PPh_3/Cs_2CO_3 system, which has

been proved to be an effective organocatalyst for boron conjugate additions to α,β–unsaturated esters and ketones, [27] did not promote the β-boration of the imine substrate (Table 2.5, entry 5).

A similar trend was observed in the β–boration of imine (*E*)-N-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (**1d**) (Table 2.5, entries 9-12) and (*E*)-N-((*E*)-4-phenylbut-3-en-2-ylidene)butan-1-amine (**1b**) (Table 2.5, entries 13-15). In these reactions, $Fe(acac)_2/PPh_3$ was the only catalyst precursor that provided complete conversion within 6 hours. Moreover, removal of the iron precursor diminished the activity completely again (Table 2.5, entries 12, 15).

Table 2.5. Influence of iron on catalytic β-boration of α,β-unsaturated imines [a].



1b: R' = Ph R'' = CH_3 R = nBu
1c: R' = Ph R'' = CH_3 R = Bn
1d: R' = Ph R'' = CH_3 R = Ph

1b: R' = Ph R'' = CH_3 R = nBu
1c: R' = Ph R'' = CH_3 R = Bn
1d: R' = Ph R'' = CH_3 R = Ph

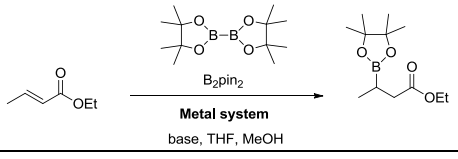
Entry	Imine	Iron system	Cs_2CO_3 (mol%)	PPh_3 (mol%)	T (ºC)	T(h)	Conv. (%) [b]
1	**1c**	$Fe(acac)_2$	15	---	70	6	28
2	”	$Fe(acac)_2$	3	4	70	6	32
3	”	$Fe(acac)_2$	9	4	70	6	74
4	”	$Fe(acac)_2$	15	4	70	6	99
5	”	---	15	4	70	6	---
6	”	$FeCl_2$	15	4	70	6	63
7	”	$Fe(OMe)_2$	15	4	70	6	38
8	”	$Fe(acac)_3$	15	4	70	6	33
9	**1d**	$Fe(acac)_2$	15	4	70	6	99
10	”	$Fe(acac)_2$	15	-	70	6	54
11	”	$Fe(acac)_3$	15	4	70	6	41
12	”	---	15	4	70	6	---
13	**1b**	$Fe(acac)_2$	15	4	70	6	99
14	”	$Fe(acac)_2$	15	-	70	6	21
15	”	---	15	4	70	6	---

[a] Standard conditions: (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine / bis(pinacolato)diboron / Fe complex = 0.5/0.55/0.01. Fe/PPh_3 = 1/2. Cs_2CO_3: mol% with respect to the substrate, MeOH: (2.5 mol%). Solvent: THF (2.5 mL). [b] Determined by ^1H NMR spectroscopy.

Current debates on the role of metal impurities in "iron-mediated" reactions [28] prompted us to carefully examine the possible effect of traces of transition metals in our iron precursors. Intending to be comprehensive, we considered all the transition metals which had ever been reported to catalyze the β–boration of any kind of α,β–unsaturated carbonyl compound. As a matter of fact, the catalyst precursor $Fe(acac)_2$ 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 α,β–unsaturated carbonyl compounds, [29,30] and beforehand we demonstrated that the copper complexes are excellent catalysts for the β–boration of α,β–unsaturated imines, as well. No other metals, known to be active in this type of reaction, such us Pt, Rh and Pd, were listed in the quality certificate of the product. To be able to draw general conclusions on the catalytic activity of iron, we chose an α,β–unsaturated ester, ethyl crotonate, as a general modle substrate. Under standard reaction conditions the concentration of the iron system is ca. $5x10^{-3}$ M, (Table 2.5, 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 $1.2x10^{-7}$ M and $9.2x10^{-7}$ 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. As a comparison, we performed reactions using CuCl and $CuOTf{\cdot}4CH_3CN$ as transtion metal precursors, as well as with $NiCl_2$ and $Ni(COD)_2$, under the standard conditions of the iron-mediated reactions and using NaO*t*Bu as base in the stock solutions due to its good solubility in THF (Table 2.6, entries 1,2,3,9,10). In subsequent experiments we gradually decreased the concentration of the *"in situ"* formed, base-activated Cu and Ni complexes from $5x10^{-3}$ M to $5x10^{-6}$ M. Both CuCl and $CuOTf{\cdot}4CH_3CN$ form considerably more active catalysts than $Fe(acac)_2$ when applied in the same concentration, $5x10^{-3}$ M (Table 2.6, entries 1, 2, 3). The higher activity is even more obvious when the catalyst concentration is decreased with one factor, to $5x10^{-4}$ M (S/Cu = 500), and the

substrate is still quantitatively converted into the product (Table 2.6, entry 4). Further decreasing the concentration of the Cu complex the conversion quickly diminishes: at $5x10^{-5}$ M copper concentration only 5% of the product can be observed, and at $5x10^{-6}$ M concentration the substrate remains intact. Under the optimised conditions for the iron-mediated β-boration reactions, nickel complexes are much less active than the copper catalysts (Table 2.6, entries 9,10). Both $NiCl_2$ and $Ni(COD)_2$ provided incomplete conversions when applied in the concentration of the iron precursor, and decreasing the concentration with one magnitude resulted in complete inactivity. Considering the high purity of the $Fe(acac)_2$ precursor (99.95%), and the activity vs. concentration profiles of the copper and nickel catalysts, one can conclude that the heavy metal impurities cannot contribute to the overall activity in the iron mediated β-boration reactions.

Table 2.6 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 [a].



Entry	Precursor	Concentration(mol.dm^{-3})	Conversion (%) [b]
1	$Fe(acac)_2$	5×10^{-3}	45
2	CuCl	5×10^{-3}	99
3	$CuOTf \cdot 4CH_3CN$	5×10^{-3}	99
4	$CuOTf \cdot 4CH_3CN$	5×10^{-4}	99
5	$CuOTf \cdot 4CH_3CN$	2.5×10^{-4}	28
6	$CuOTf \cdot 4CH_3CN$	1.25×10^{-4}	17
7	$CuOTf \cdot 4CH_3CN$	5×10^{-5}	5
8	$CuOTf \cdot 4CH_3CN$	5×10^{-6}	0
9	$NiCl_2$	5×10^{-3}	53
10	$Ni(COD)_2$	5×10^{-3}	51
11	$Ni(COD)_2$	$5 \times (10^{-4} - 10^{-6})$	0

[a] Standard conditions: ethylcrotonate = 0.5 mmol, bis(pinacolato)diboron = 0.55 mmol, Metal/PPh_3/NaO^{t}Bu = 1/2/5, T= 70ºC, t= 6h. MeOH (2.5 mol%). Solvent: THF (2 mL). [b] Determined by G.C.

In the last years, the organocatalytic β–boration of α,β–unsaturated carbonyl compounds have been developed. [27,31] In this context, we explored deeper insight into the role of Fe in the β–boration reactions. Remarkably, the Fe-free system alone cannot promote the conjugate β–addition to the α,β–unsaturated imines (Table 2.5, entries 5,12,15) but complete conversions were observed when base was present (Table 2.5, entries 4, 9, 13). These results nicely demonstrate the benefits of the iron salts in the β–boration reaction. Two possibilities have been explored to determine exactly the role of Fe:

a) An iron complex activates the diboron reagent forming Fe-B bonds (by oxidative addition [32] or transmetallation) and the formed iron-boryl complex promotes the B-addition to the electron deficient olefins in the *inner* coordination sphere.

b) The substrate is activated by the iron salt through a Lewis acid-base interaction between the metal and the carbonyl or imino group, which polarizes the conjugated π-electron system of the substrate and facilitates the B-addition.

Towards this end, we conducted a systematic NMR study to monitor the possible formation of iron-boryl complexes under catalytic conditions (*a*: 1eq $Fe(acac)_2$+1eq B_2pin_2, *b*: 1eq $Fe(acac)_2$+1eq B_2pin_2+1eq NaO^tBu, *c*: 1eq B_2pin_2+1eq NaO^tBu). The main conclusion of the study is that under catalytic conditions the diboron reagent is only affected by the base, independently of the presence or absence of $Fe(acac)_2$.

In order to study possible interactions between the iron precursors and the substrates, we have performed the ESI-MS^+ analysis of solutions of $Fe(acac)_2$ and $Fe(acac)_3$ in the presence of the model substrate **1c**. In the case of the combination $[Fe(acac)_2]$/**1c**, the molecular ion $[Fe(acac)_2]^+$-**1c** was clearly observable (Figure 2.4).

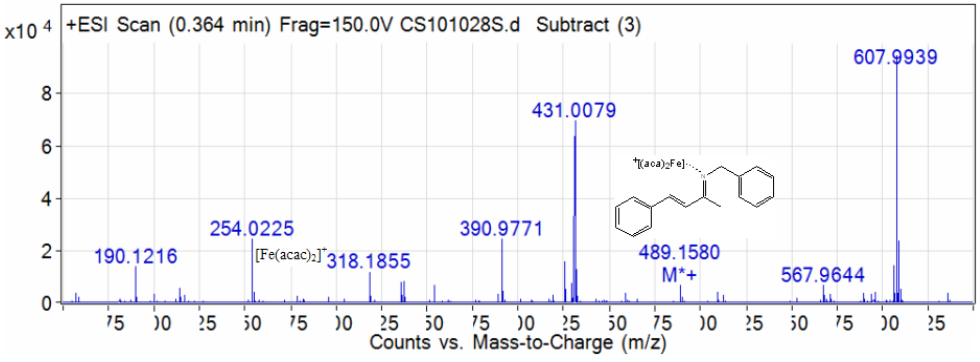


Figure 2.4 ESI-MS$^+$ analysis of $Fe(acac)_2$ and (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine (**1c**).

$[Fe(acac)_2]$ and the corresponding adduct with **1c** is oxidized under the conditions of the ESI-MS$^+$ analysis, which leads to the observation of the corresponding $[Fe(acac)_2]^+$, $[Fe(acac)_2]^+$-**1c** molecular ions. The 17e$^-$ $Fe(acac)_3$ precursor could be observed both as $[Fe(acac)_2]^+$ and $[Fe(acac)_3+Na]^+$ by ESI-MS$^+$. Naturally, this precursor needs to lose a ligand to act as a Lewis acid. Accordingly, the $[Fe(acac)_2]^+$-**1c** adduct could be clearly observed (Figure 2.5).

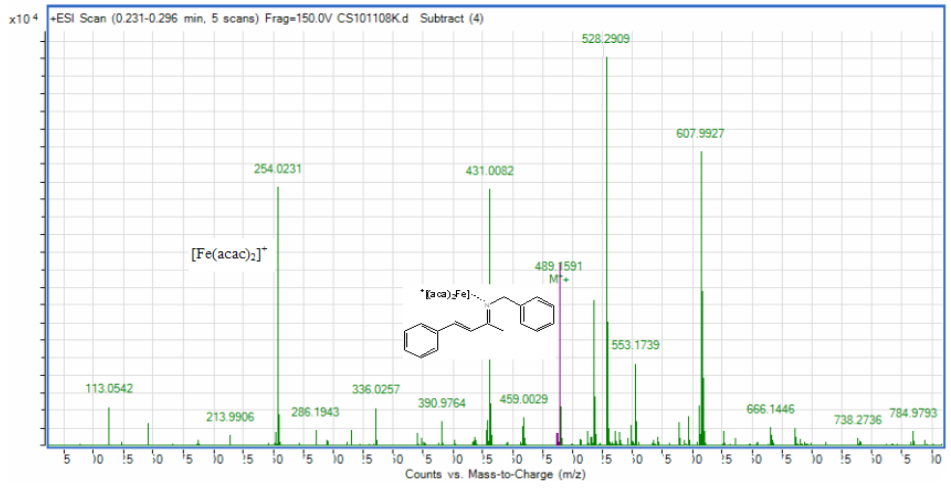
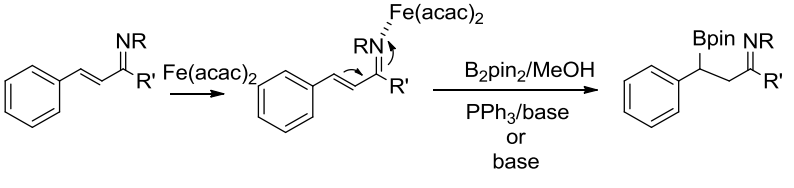


Figure 2.5 ESI-MS$^+$ analysis of the solutions of $Fe(acac)_3$ and (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine (**1c**) wherein the $Fe(acac)_3$ lose a ligand to form the adduct $[Fe(acac)_2]^+$-**1c**.

It is worthnoting that the analogous $[Fe(acac)_2]^+$-chalcone adduct has also been observed in the $FeCl_3$/acac-catalyzed Friedel-Crafts alkylation of indoles [33].

Based on these experimental results we suggest a preactivation of the substrates by the Lewis acidic Fe(II) and Fe(III) salts (Scheme 2.23), as it has been proposed for the iron-catalyzed Michael additions and other conjugate addition reactions [34]. The boron nucleophile is generated upon the interaction of the bis(pinacolato)diboron and the base. [31b] Thus, the reaction is facilitated by two catalytic systems which function independently. The synergic effect of the transition metal and organocatalytic system is particularly striking in the case of the imine substrates. Neither the iron salt nor the base alone can promote the reaction, however, their combination leads to complete conversions.



Scheme 2.23 The postulated role of iron in the β–boration of α,β–unsaturated imines.

2.6 Conclusions

Initial attempts to convert C-B bonds into C-N bonds with retention of the configuration were not successful. However, a new strategy has been developed to accomplish the same target product formation. This involved the β-boration of α,β–unsaturated imines, carried out for first time in this work.

It should be emphasized that the synthesis of the α,β–unsaturated imines is not obvious due to the competitive aza-Michael addition. Despite this fact we have succeeded in the synthesis of ten α,β–unsaturated imines possessing different electronic and steric properties.

The first copper-catalyzed β–boration of α,β–unsaturated imines, has been successfully developed under mild reaction conditions. It is important to mention that remarkably high enantioselectivities (up to 99 *ee*%) have been induced in the formation of the new C-B bond using copper salts modified with chiral phosphine ligands. This methodology permits the synthesis of enantionenriched β–boryl imines that can be used as intermediates for the synthesis of chiral γ–amino alcohols.

We have shown that iron salts also facilitated the β–boration of α,β–unsaturated imines although the iron assisted reactions were less efficient than the copper (I) mediated reactions. From a mechanistic point of view, we postulated that Fe salts activate the α,β–unsaturated imines and facilitate the nucleophilic attack of B_2pin_2 with base / MeOH.

2.7 References

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Chapter 3: One-pot routes to synthesize enantioenriched γ-amino alcohols

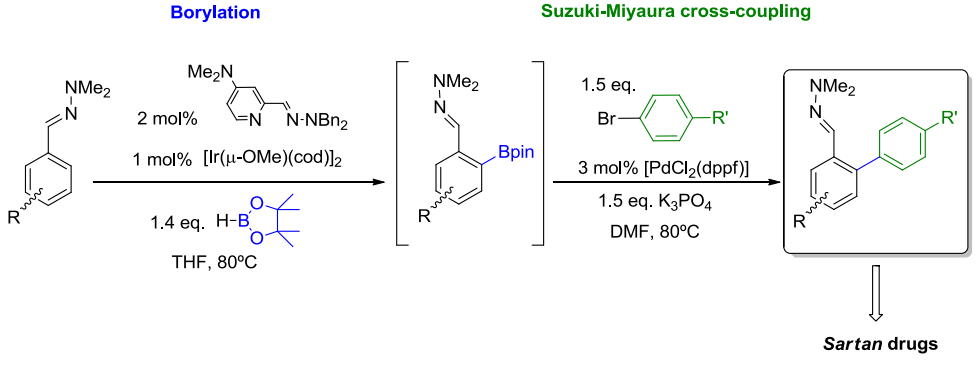
Table of contents

3.1 Introduction

The total synthesis of natural products or biologically active compounds often is not an easy strategy. Different steps are required to achieve the desired complex molecular structure.

Performing two or more steps in one-pot would allow to avoid complicated separation processes or purifications of the intermediate chemical compounds thus, saving time and resources and usually increasing the overall yield. For this reason, the one-pot synthesis is considered an ecologically and economically efficient way of working, to be followed by synthetic chemists.

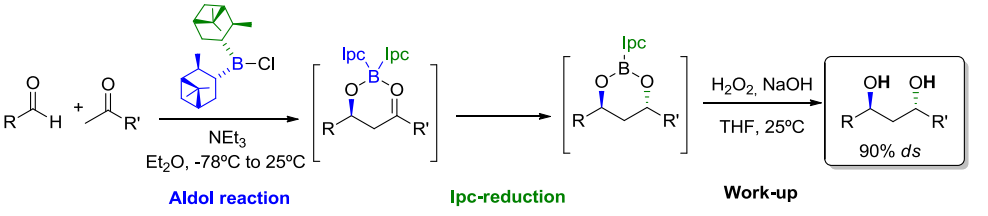
The fact that the boryl group usually can be replaced easily by another functional group renders the application of organoboranes very attractive in one-pot synthesis. Recently, Lassaletta and coworkers developed a very efficient one-pot selective borylation/Suzuki-Miyaura cross-coupling process. [1] They were able to obtain functionalized biphenyl derivatives that have been transformed into valuable intermediates for the synthesis of modified *Sartan* type drugs (Scheme 3.1).



Scheme 3.1 One-pot borylation/Suzuki-Miyaura cross-coupling to the synthesize *Sartan* drug derivates.

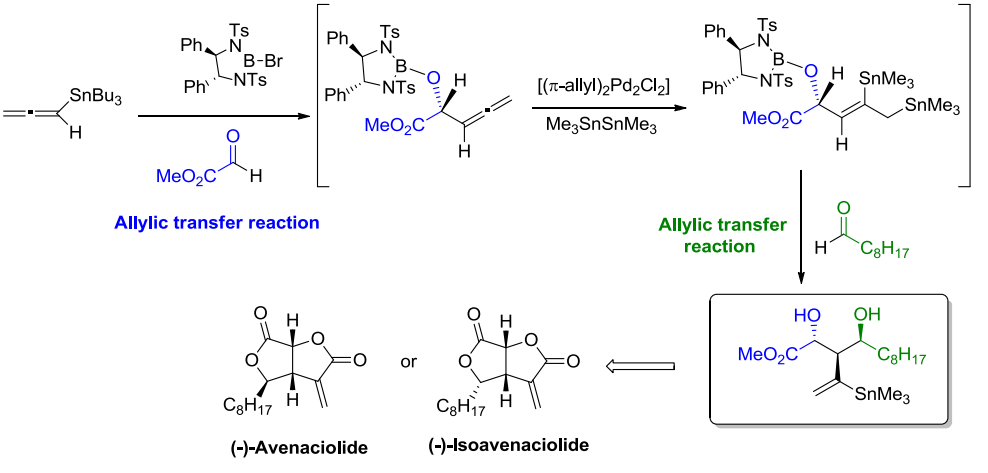
Moreover, several very efficient one-pot processes have been developed for the synthesis of 1,3-difunctionalized molecules.

Stereoselective synthesis of 1,3-anti diols using an aldol-coupling/reduction sequence have been carried out by Menche and coworkers. [2] They generated two new stereogenic centers with around 90% *anti*-selectivity (Scheme 3.2).



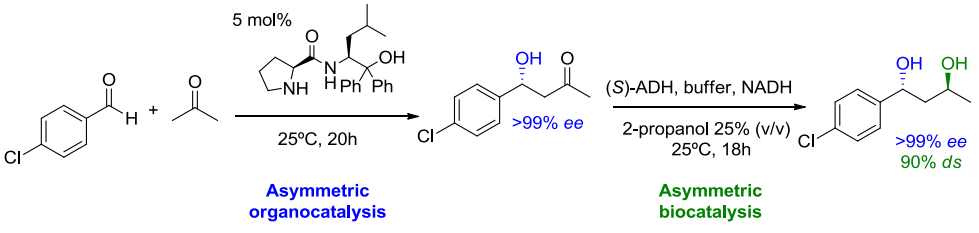
Scheme 3.2 One pot aldol-coupling/reduction sequence to synthesize 1,3-*anti* diols.

Jung and coworkers were able to obtain enantiomerically enriched 2-(1-stannylvinyl)-1,3-diols by a sequential allylic transfer/distannylation process. [3] The approach is important and useful, therefore it has successfully been applied for the syntheses of the antibacterial (-)-avenaciolide and (-)-isoavenaciolide (Scheme 3.3).



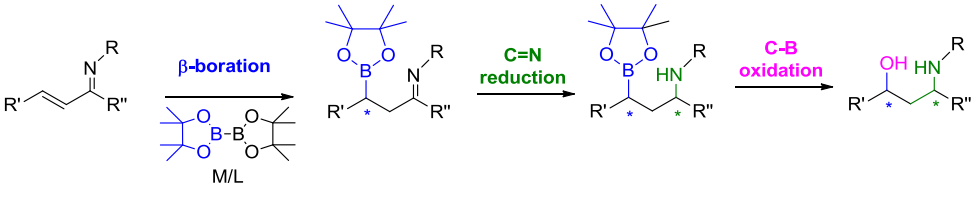
Scheme 3.3 Asymmetric allylic transfer/distannylation one-pot reaction sequence for the synthesis of precursors of (-)-avenaciolide and (-)-isoavenoaciolide.

Biocatalytic reactions are also commonly used in one-pot sequences. Recently, the combination of an asymmetric organocatalytic and an enzyme catalyzed reaction provided the synthesis of 1,3-diols with total control of the diastereoselectivity (Scheme 3.4). [4]



Scheme 3.4 Synthesis of 1,3-*anti*-diols by organo- and biocatalysis.

Taking into consideration the advantages of one-pot reaction sequences, we decided to develop such a methodology to synthesize γ–amino alcohols based on three reactions: β–boration/reduction/oxidation (Scheme 3.5).



Scheme 3.5 Proposed one-pot synthetic route towards γ–amino alcohols.

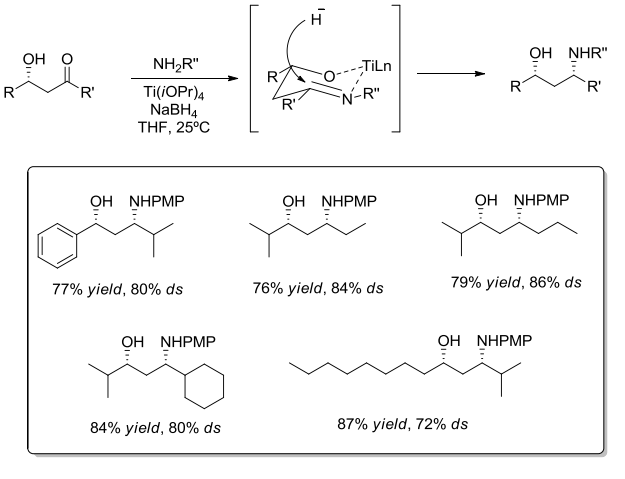
The first step of the sequential process, the β–boration of α,β–unsaturated imines, has been described in Chapter 2. The two following steps, the reduction of the C=N bond and the oxidation of C-B, will be explored in this Chapter.

3.2 The origin of the diastereoselective control in the *in situ* reduction/oxidation of β–boryl imines

The next steps of the synthetic pathway towards accessing γ–amino alcohols were the 1,3-diastereocontrolled reduction of the C=N bond and the subsequent oxidation of the C(Bpin) to C(OH).

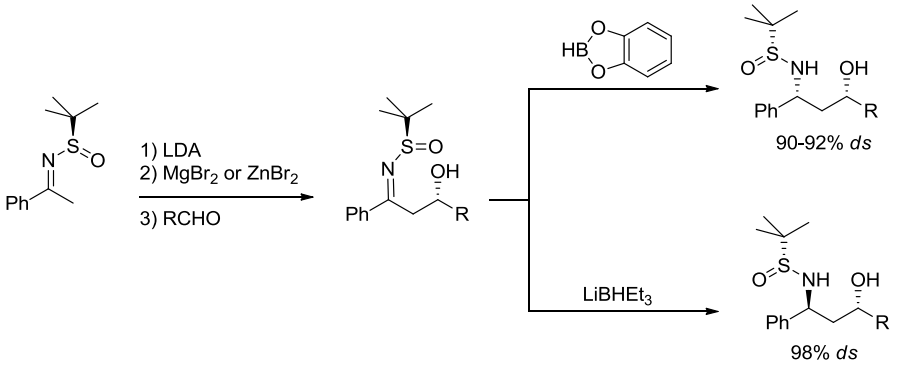
Although much is known about the asymmetric hydrogentation of alkenes and ketones catalyzed with chiral transition metal complexes, the asymmetric hydrogenation of prochiral C=N has received less attention. The first attempts to hydrogenate prochiral imines were made with Rh(I) complexes of chiral phosphines. [5] However, later on it was found that ruthenium [6] and iridium [7] complexes provided higher activities and enantioselectivities. For this reason, we first tried to reduce the C=N bond using $[Rh(nbd)_2(BINAP)]PF_6$, $[Ru(Cl)_2(BINAP)(NH_2CH_2CH_2NH_2)]$ and also $[Ir(cod)(BINAP)]BF_4$ complexes. Although, relatively high temperatures (up to 70 ºC) and high pressures (up to 20 atm) were used, no hydrogenated product was observed. As an alternative solution, stoichiometric reducing agents were considered to reduce the C=N double bond.

It has been reported in the literature that Rudolph and coworkers have developed a methodology for the direct reductive amination of β-hydroxy-ketones to access *syn*-1,3-amino alcohols. [8] In that work, the imino functionality is formed "*in situ*" in the presence of a primary amine and reduced subsequently using $NaBH_4$. The imino alcohol intermediate was proposed to strongly coordinate to $Ti(OiPr)_4$, leading to the desired 1,3-*syn* product with 62-86% diastereoselectivity (Scheme 3.6). [8]



Scheme 3.6 Postulated directed reductive amination of β–hydroxy-ketones by Rudolph and coworkers.

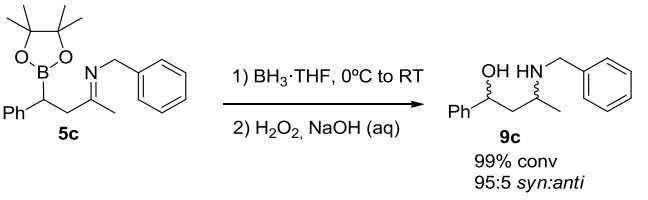
Another methodology was reported by Ellman and coworkers. [9] They used a chiral imino group as auxiliary to control the asymmetric aldol reaction between the chiral imine and a variety of aldehydes. The actual nucleophile in these reactions is the metalloenamine generated from the imine with $MgBr_2$ or $ZnBr_2$ additives. The reduction of the resulting β-hydroxysulfinyl imines with catecholborane and $LiBHEt_3$ provided *syn*- and *anti*-1,3-amino alcohols, respectively, with very high diastereoisomeric ratios (Scheme 3.7).



Scheme 3.7 Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols from chiral N-sulfinyl imines.

However, Whiting and coworkers [10] were pioneers in reducing the C=N double bond with boronate esters functionality in the β position using BH_3·THF and chiral reducing agents. Consequently, we thought that the best way to investigate the potential reduction of β–boryl imine would be in collaboration with the Whiting's group (Durham University).

Initially the reduction was explored in the organoboronate ester β–boryl benzylimine (**5c**) with BH_3·THF. Subsequent oxidative cleavage of the C-B bond in the presence of alkaline hydrogen peroxide yielded the desired amino alcohol product (**9c**). The complete conversion was confirmed by ^{1}H NMR (Table 3.1, entry 1) (Scheme 3.8).



Scheme 3.8. *In situ* reduction and oxidation of β–boryl benzylimine (**5c**) using BH_3·THF as a reducing agent.

Analysis of the ^{1}H NMR spectrum of the γ–amino alcohol **9c** indicated a 95:5 mixture of diastereomeric products by two peaks at 4.9 and 4.7 ppm corresponding to the CH-OH of the *syn* and *anti* products, respectively (Figure 3.1a). Moreover, HPLC-UV experiments also confirmed the diastereoselectivity observed by ^{1}H NMR (Figure 3.1b) (Table 3.1, entry 1).

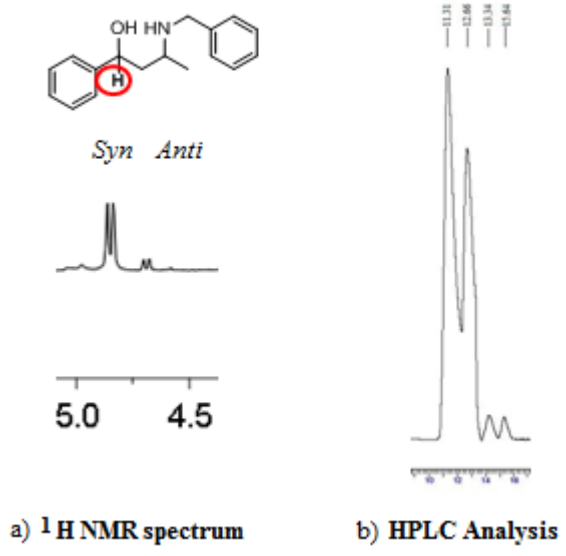
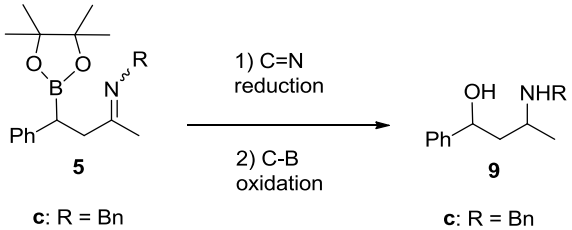


Figure 3.1 Diastereoselectivity of γ–amino alcohol **9c** determined by a)^{1}H NMR spectrum and b) HPLC-UV analysis.

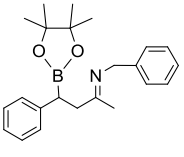
The reducing agent sodium borohydride in EtOH has been reported to give improved stereoselectivity at low temperatures in some cases, [11] however, in our case, both the conversion and the diastereoselectivity decreased compared to BH_3·THF (Table 3.1, Entry 2).

Faul and co-workers highlighted the influence of the solvent on *syn*:*anti*-diastereoisomer ratios in the reduction of sulfinamides using $NaBH_4$. [12] Inspired by these examples, we also carried out reductions of **5c** with $NaBH_4$ in wet THF and MeOH. While $NaBH_4$ in wet THF produced similar results to those obtained with $NaBH_4$ in EtOH (Table 3.1, entry 3), the reduction in MeOH gave the *anti*-diastereoisomer with high selectivity (Table 3.1, entry 4).

Table 3.1. 1,3-Diastereocontrolled reduction of the C=N bond in the β-boryl imines **5c** followed by C-(Bpin) oxidation [a].

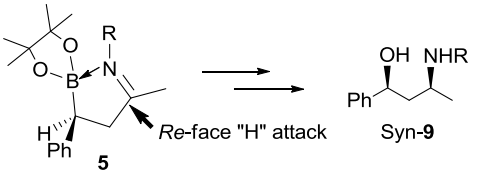


5 **c**: R = Bn **9** **c**: R = Bn

Entry	β-boryl imine	Reducing Reagent	Conv (%) [b] (% *I.Y.)*	*Syn/anti* ratio [c] (*syn:anti* isolated)
1	 **5c**	BH_3·THF	100 (82)	95:5 (99:1)
2	„	$NaBH_4$·EtOH	83	62:38
3	„	$NaBH_4$·THF(2%wet)	69	70:30
4	„	$NaBH_4$·MeOH	53 (35)	16:84(1:99)
5	„	DIBAL-H·THF	80	78:22
6	„	DIBAL-H, $ZnCl_2$ THF	73	79:21

[a] Standard conditions: 3.0 eq. of reducing agent, followed by the addition of $NaOH/H_2O_2$(aq.) in excess; further details in SI. [b] Conversion calculated by 'H NMR spectroscopy. [c] *Syn:anti*-ratio determined by HPLC analysis.

Importantly, even the bulkiest hydride source DIBAL-H, favoured the formation of the *syn*-product (Table 3.1, entry 5). To explain the highly selective formation of the *syn*-isomer, we considered the cyclic form of **5c** formed by an intramolecular B←N Lewis acid-base interaction, consistent with the lower ^{11}B NMR chemical shift ($CDCl_3$, δ=22.3 ppm) in comparison with the ^{11}B NMR chemical shifts of β–boryl esters or ketones ($CDCl_3$, δ=31-36 ppm). [13] In contrast to the open chain form of **5c**, the less hindered side of the cyclic structure is the *re-f*ace of the imine (see Scheme 3.9). Upon nucleophilic attack of a hydride reagent from the *re*-face of the B←N cyclic imine, the *syn*-product is formed, in accordance with our experimental results. It is important to note that the addition of the Lewis acid $ZnCl_2$ to the DIBAL-H system, which in principal could compete for the Lewis-base imino group and open the cyclic structure, did not alter the diastereoselectivity of the reduction (Table 3.1, entry 6).



Scheme 3.9 Intramolecular B←N Lewis acid-base interaction that could determine the relative stereocontrol to give the *syn*-diastereoisomer.

To get more insights into the reversed selectivity observed in the case of the reduction carried out with sodium borohydride in MeOH (Table 3.1, entry 4), we recorded the ^{11}B NMR spectrum of **5c** in all the solvents used in the reduction process. In all solvents which facilitated the formation of the *syn*-product (including in EtOH), we observed one single ^{11}B NMR resonance with very similar chemical shifts to that found in $CDCl_3$ (*i.e.* 21.8-22.3 ppm) indicative of a B←N intramolecular interaction. In contrast, the ^{11}B NMR spectrum of **5c** in MeOH, the only solvent that reversed the selectivity and favoured the formation of the *anti*-isomer, displayed a new resonance at 18.9 ppm, besides the original signal at 22.3 ppm (Figure 3.2).

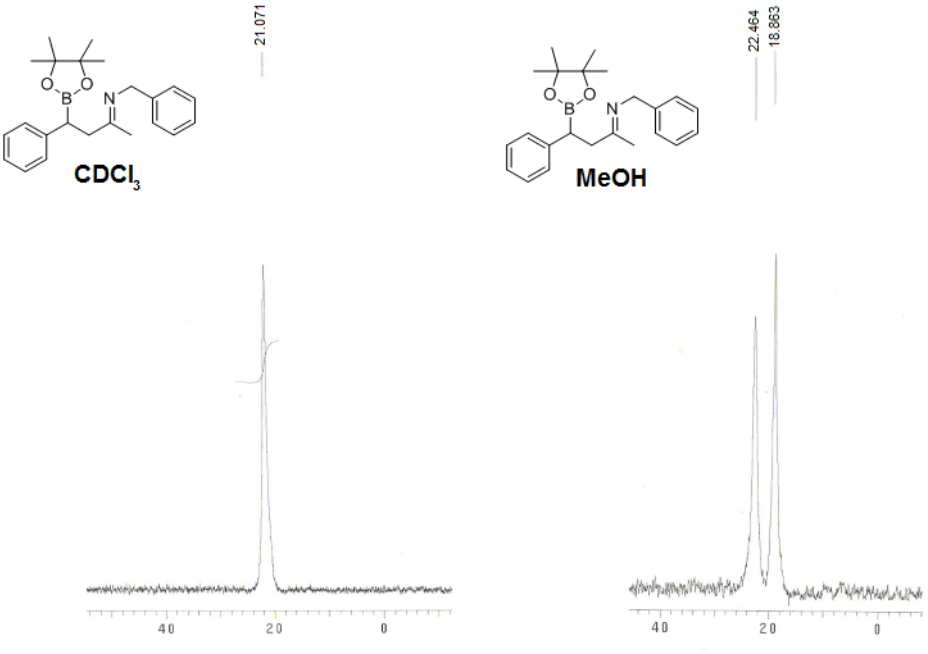


Figure 3.2 The ^{11}B NMR spectrum of **5c** in $CDCl_3$ and MeOH.

In pure MeOH ([**5c**] = 0.25 M, RT) the ratio of the cyclic form **5c** and the new species was 53:47. The formation of the new species, most likely a MeOH-**5c** adduct, is reversible and the ratio of the cyclic form of **5c** and the MeOH-**5c** adduct depends on both the concentration of the MeOH and the temperature at constant [**5c**]. Therefore, recording the ^{11}B NMR spectrum in $CDCl_3$:MeOH, we could observe the new species at a MeOH concentration of as low as 1.5 M, which represents a ratio (MeOH to **5c**) of 6. Under these conditions, at room temperature, 3 mol% of cyclized **5c** was converted into the MeOH-**5c** adduct. The conversion increases with the concentration of the MeOH up to 47%, as observed in the neat alcohol (Figure 3.3).

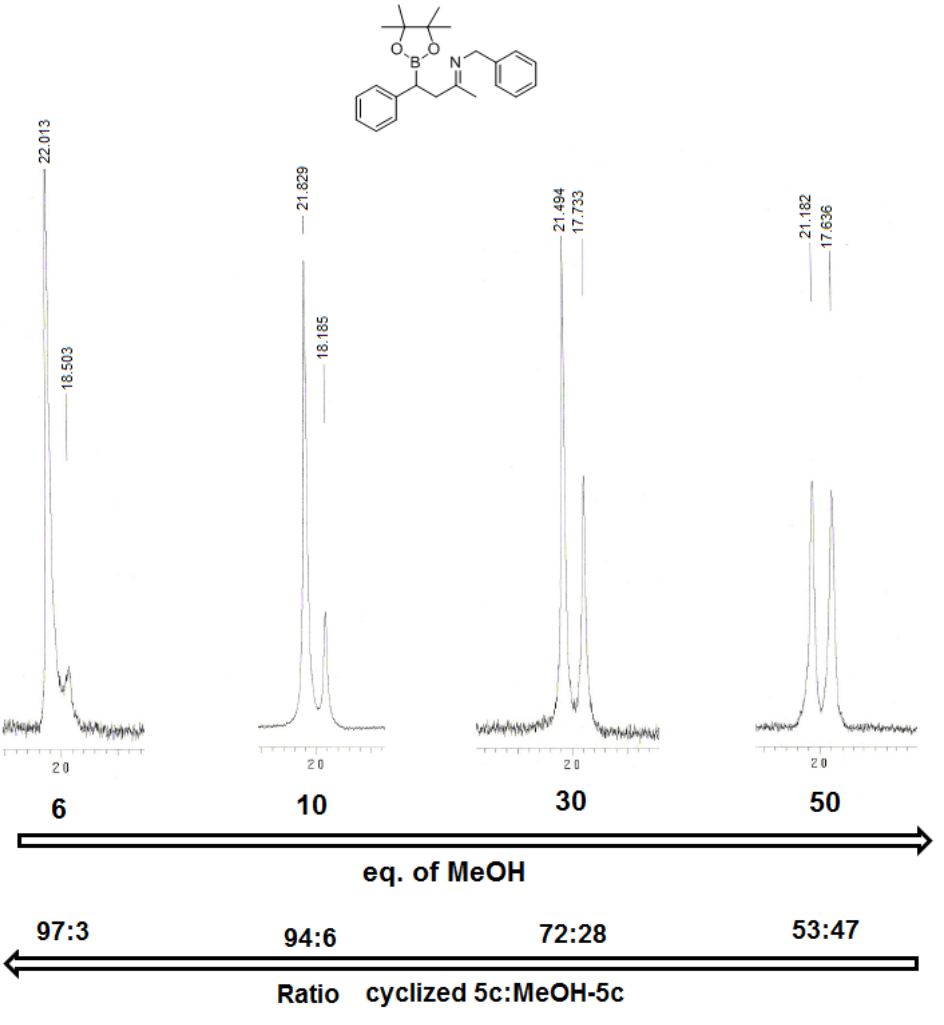


Figure 3.3 The ^{11}B NMR spectrum of **5c** with different equivalents of MeOH.

The MeOH-**5c**: cyclic **5c** ratio further increases upon decreasing the temperature; at 223 K, the ratio reaches *ca.* 70:30 (Figure 3.4).

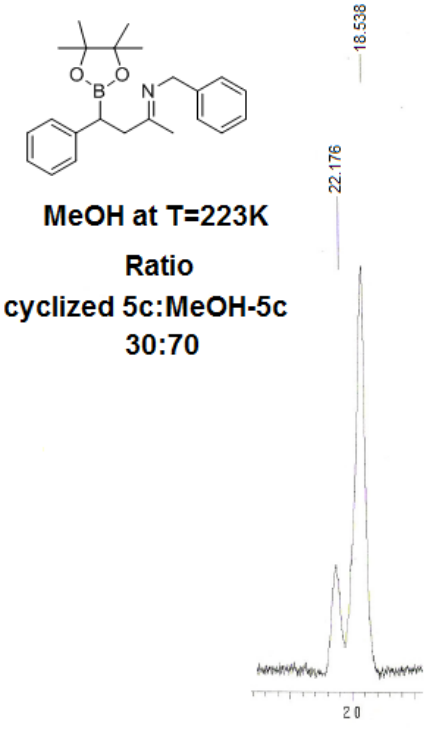


Figure 3.4 The ^{11}B NMR spectrum of **5c** in MeOH at T =223K.

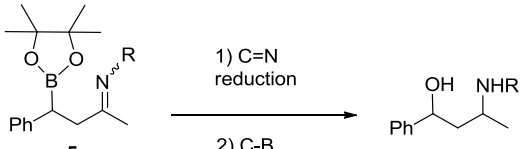
We do not have direct evidence of the exact structure of the MeOH-**5c** adduct, however, its ^{11}B NMR chemical shift and related literature data [14] suggest that the interaction between the MeOH and **5c** might involve both H-bonds and Lewis acid-base interactions. Independently of the exact nature of the borylated imine-MeOH interaction, the net result is the cleavage of the weak B←N bond and the formation of the *anti*-diastereoisomer upon hydride attack, presumably resulting from an acyclic stereoselection process.

The same reducing agents and conditions were then examined in the reduction of the β–boryl imines **5b** and **5d** to determine if the structure of the imino group has an influence on the diastereoselectivity. The reduction of β–boryl phenylimine **5d** gave similar results to those obtained in the reduction of **5c**. Very highy, practically complete, *syn* selectivity was observed when BH_3·THF was used as reducing

agent, while predominantly the *anti*-diastereoisomer was formed when the reduction was carried with $NaBH_4$ in MeOH (Table 3.2, entries 1 and 4, respectively). The reduction with $NaBH_4$ in THF (2% H_2O) and $NaBH_4$ in EtOH also afforded the *syn*-isomer with high selectivity (Table 3.2, entries 2 and 3). Among the reducing agents DIBAL-H provided the lowest diastereoselectivity (72% *syn*), similar to the one observed for substrate **5c**.

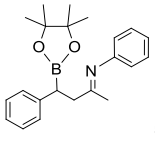
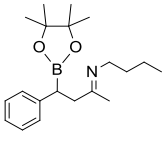
A pronounced tendency for the formation of the *syn*-isomer was observed in the reduction/oxidation sequence of β–boryl butylimine **5b** (Table 3.2, entries 7-12), even when $NaBH_4$ in MeOH was the reducing agent. Importantly, three of the reducing agents provided complete diastereoselectivity, however, a mixture of isomers was observed when in the case of BH_3·THF (Table 3.2, entry 7).

Table 3.2. 1,3-Diastereocontrolled reduction of the C=N bond in the β-boryl imines **5**b and **5d** followed by C(Bpin) oxidation [a].



5
b: R = nBu
d: R = Ph

9
b: R = nBu
d: R = Ph

Entry	β-boryl imine	Reducing Reagent	Conv (%) [b] (% *I.Y.*)	*Syn/anti* ratio [c] (*syn:anti* isolated)
1	 **5d**	BH_3·THF	>99(95)	99:1(99:1)
2	„	$NaBH_4$·EtOH	>99	93:7
3	„	$NaBH_4$·THF(2%wet)	>99	82:18
4	„	$NaBH_4$.MeOH	>99(30)	10:90(1:99)
5	“	DIBAL-H THF	78	72:28
6	„	DIBAL-H, $ZnCl_2$ THF	76	73:27
7	 **5b**	BH_3·THF	>99(20)	54:46(1:99)
8	„	$NaBH_4$·EtOH	89	81:19
9	„	$NaBH_4$·THF(2%wet)	86	83:17
10	„	$NaBH_4$·MeOH	66	99:1
11	„	DIBAL-H THF	90(84)	99:1(99:1)
12	„	DIBAL-H, $ZnCl_2$ THF	86	99:1

[a] Standard conditions: 3.0 eq. of reducing agent, followed by the addition of $NaOH/H_2O_2$(aq.) in excess; further details in SI. [b] Conversion calculated by 'H NMR spectroscopy. [c] *Syn:anti*-ratio determined by HPLC analysis.

In summary, the most remarkable finding was a strong dependence of the reducing agent in the diastereoselective reduction of β–boryl imines. Generally, in the case of β–boryl benzylimine **5c** and β–boryl phenylimine **5d**, the *syn*-isomers are formed when the BH_3·THF is used; while, the best reducing agent to obtain the *anti*-isomer is $NaBH_4$/MeOH (Figure 3.5). On the other hand, in the case of the β–boryl butylimine **5b** the best *syn*-selectivity can be obtained with DIBAL-H or $NaBH_4$/MeOH, rather than with BH_3·THF. This fact suggests that the nature of the imino group also has significant influence on the diastereoselectivity of the reduction (Figure 3.5).

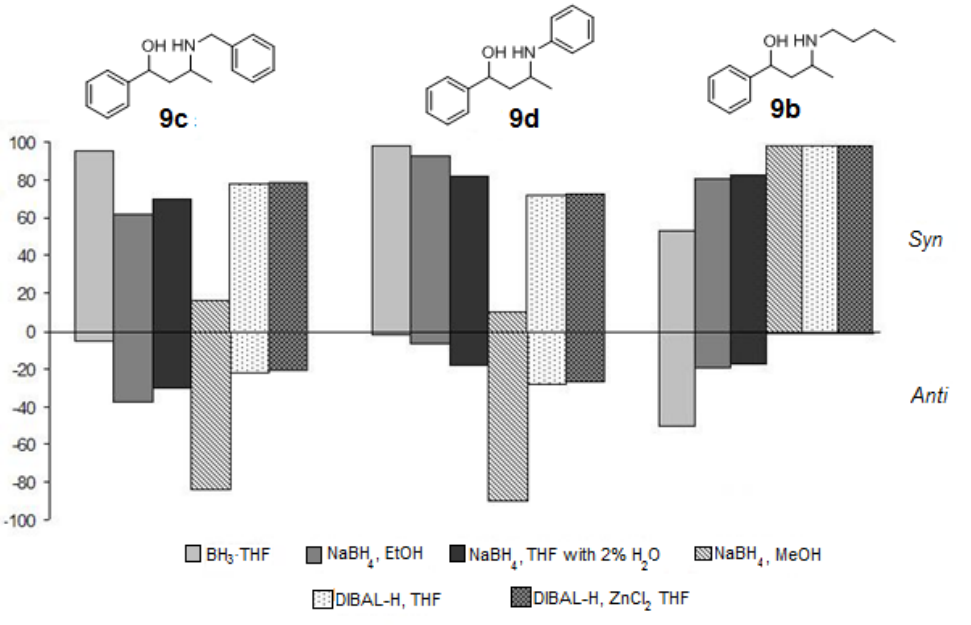
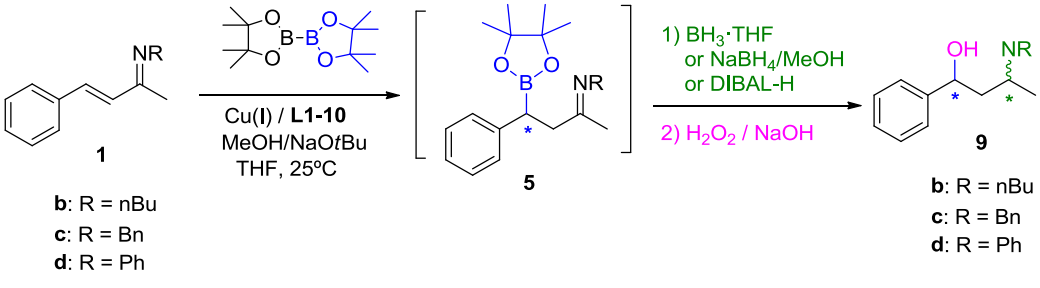


Figure 3.5 1,3-Diastereocontrol in the reduction/oxidation process of β–boryl imines **5** towards the synthesis of γ–amino alcohols **9**.

3.3 Asymmetric copper-catalyzed β-boration/reduction/oxidation of α,β-unsaturated imines: the one-pot approach

Once the diastereoselective reduction/oxidation protocol had been optimized for both the *syn*- and *anti*-diastereoisomers, our last goal was to develop a

stereoselective one-pot β-boration/reduction/oxidation process to synthesize the desired enantio- and diastereo-enriched γ–amino alcohols. Since the conditions of each step had been established for the α,β–unsaturated imines **1b**,**1c** and **1d**, we expected to be able to maintain both the activity and the selectivity of all three reactions in the one pot process (Scheme 3.10) and, then, extend the one-pot method to others α,β–unsaturated compounds.

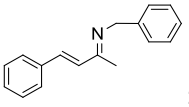
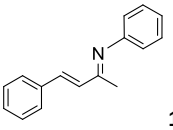


Scheme 3.10 Stereoselective one-pot β–boration/reduction/oxidation of **1** to synthesize chiral enanrioched γ–amino alcohols **9**.

To this end, the asymmetric β-boration of **1b, 1c** and **1d** with Cu(I)/**L1-L10,** which was developed in the Chapter 2, was performed again but followed by *"in-situ"* reduction/oxidation of the enantioenriched **5b, 5c** and **5d**, using those reducing agents that had provided the corresponding γ-amino alcohols with the best diastereoselectivities (Table 3.1 and 3.2). The α,β-unsaturated imines **1b** (Table 3.4), **1c** and **1d** (Table 3.3) were converted into the enantioenriched γ–aminoalcohols in good to excellent yields.

The enantiomeric excess of **9c** and **9d** (Table 3.3, Figure 3.6) are comparable to the high enantiomeric excess of **5c** and **5d** (see Chapter 2 section 2.4, Table 2.3), confirming that the oxidation of C-Bpin takes place with complete retention of the configuration.

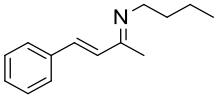
Table 3.3 Enantioselective one-pot Cu(OTf)/**L1-L10** mediated β-boration/reduction/oxidation process to obtain enantioenriched γ–amino alcohols **9c** and **9d** [a].

Entry	Imine	L	Red. Agent	Yield(%) [b] (% *I.Y.*) [c]	*Syn:anti* [b] (*syn:anti* isolated)	*e.e.* (%) [d]
1	 **1c**	**L1**	BH_3·THF	84	88:12	75
2	„	**L2**	„	>99	93:7	91
3	„	**L3**	„	>99	93:7	96
4	„	**L4**	„	>99(90)	91:9 (99:1)	99[e]
5	„	**L4**	$NaBH_4$·MeOH	>99[f] (67)	17:83 (1:99)	99[g]
6	„	**L5**	BH_3·THF	>99	89:11	76
7	„	**L6**	„	>99	92:8	83
8	„	**L7**	„	36	91:9	88
9	„	**L8**	„	>99	83:17	49
10	„	**L9**	„	>99	91:9	74
11	„	**L10**	„	>99	91:9	71
12	 **1d**	**L1**	„	66	99:1	88
13	„	**L2**	„	61	99:1	57
14	„	**L3**	„	79	99:1	39
15	„	**L4**	„	>99	99:1	52
16	„	**L5**	„	66	99:1	30
17	„	**L6**	„	66	99:1	28
18	„	**L7**	„	67	99:1	66
19	„	**L8**	„	56	99:1	19
20	„	**L9**	„	>99(69)	99:1(99:1)	92[h]
21	„	**L10**	„	66	99:1	61

[a] Standard conditions: β-boration = 0.2 mmol substrate, 2 mol% Cu(OTf), 4/2 mol% mono/bidentate ligand, 1.1 B_2pin_2, NaO*t*Bu (9 mol%), MeOH (2 eq), THF (1 mL), 25 ºC, 6 h; reduction/oxidation = 3.0 eq. of reducing agent, followed by the addition of $NaOH/H_2O_2$(aq.) in excess. [b] Yield by 'H NMR spectroscopy. [c] 0.5 mmol substrate, standard conditions. [d] Determined by HPLC analysis. [e] $[\alpha]_D^{23}$= -12.34 (c 0.54 in $CHCl_3$). [f] Reducing reaction time = 18h . [g] $[\alpha]_D^{23}$= 33.3 (c 0.20 in $CHCl_3$). [h] $[\alpha]_D^{23}$ – 40.8 (c 1.14 in $CHCl_3$).

In the Chapter 2, we were not able to determine the enantiomeric excess of the β–boryl imine **5b**, but the analysis of the corresponding γ–amino alcohol **9b** clearly showed that the copper mediated β-boration of **1b** also proceeded with excellent enantioselectivities. In particular, the in *situ* formed copper-complexes of Taniaphos (**L2**) and the monodentate phosphoramidite (**L9**) performed very well (*e.e* 93% and 89%, respectively, Table 3.5, entries 2, 9).

Table 3.4 Enantioselective one-pot Cu(OTf)/**L1-L10** mediated β-boration/reduction/oxidation process to obtain enantioenriched γ–amino alcohols **9b** [a].

Entry	Imine	L	Red. Agent	Yield(%) [b] (% *I.Y.*)[c]	*Syn:anti* [b] (*syn:anti* isolated)	*e.e.* (%) [d]
1	 **1b**	**L1**	DIBAL-H	81	99:1	75
2	„	**L2**	„	96(92)	99:1(99:1)	93[e]
3	„	**L3**	„	83	99:1	25
4	„	**L4**	„	94	99:1	80
5	„	**L5**	„	94	99:1	44
6	„	**L6**	„	91	99:1	35
7	„	**L7**	„	91	99:1	55
8	„	**L8**	„	71	99:1	71
9	„	**L9**	„	90	99:1	89
10	„	**L10**	„	89	99:1	53

[a]Standard conditions: β-boration = 0.2 mmol substrate, 2 mol% Cu(OTf), 4/2 mol% mono/bidentate ligand, 1.1 B_2pin_2, NaO*t*Bu (9 mol%), MeOH (2 eq), THF (1 mL), 25 ºC, 6 h; reduction/oxidation = 3.0 eq. of reducing agent, followed by the addition of $NaOH/H_2O_2$(aq.) in excess. [b] Yield by 'H NMR spectroscopy. [c] 0.5 mmol substrate, standard conditions. [d] Determined by HPLC analysis. [e] $[\alpha]_D^{23}$ = 41.6 (c 0.8 in $CHCl_3$).

It is also interesting to note that while in the case of **1c** and **1d** the ligands generally provided the same enantiomer of the corresponding boryl imine **5c** and **5d**, the ligand effect in the β-boration of **1b** was much more dramatic, resulting in

the formation of the opposite enantiomer as the major product in several cases (Figure 3.6).

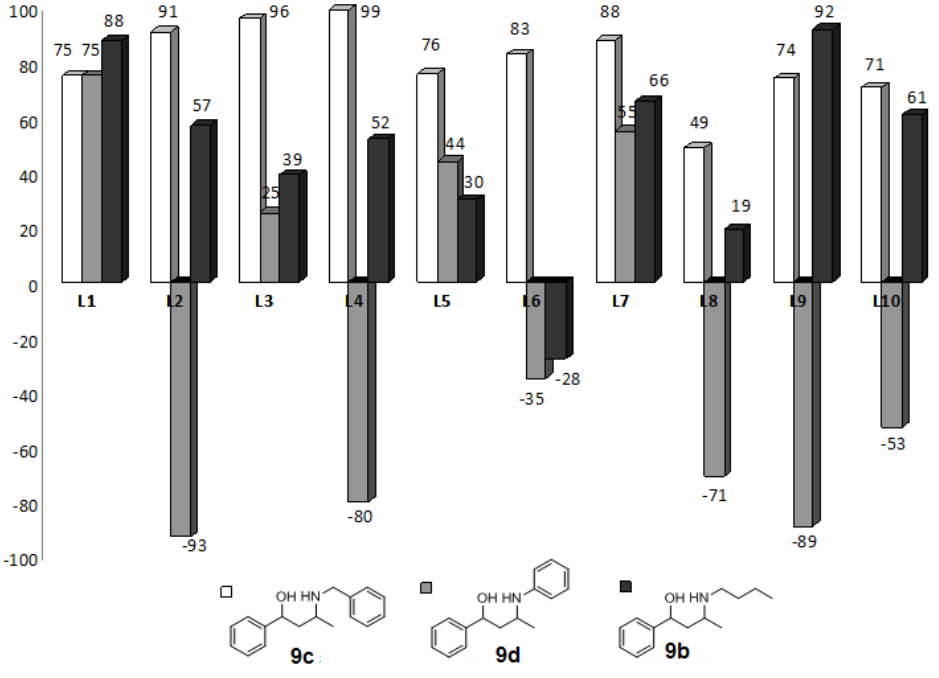
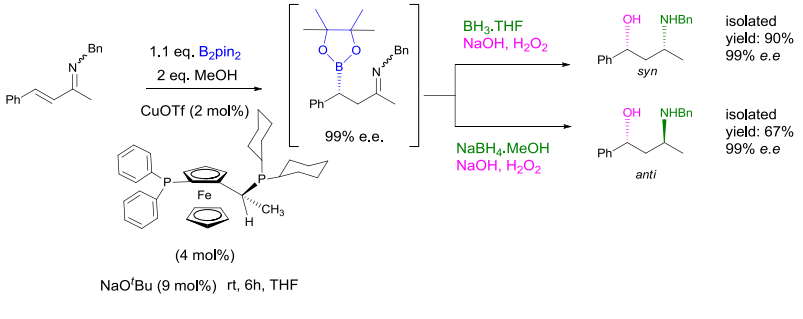


Figure 3.6 Enaniomerically enriched mixtures of γ–amino alcohols.

The diastereoselectivities in the one-pot reaction sequence were very similar to those achieved with the racemic β-boryl imines (Table 3.1 and 3.2). Consequently, we could easily synthesize the *syn*-γ–amino alcohol **9c** by β-boration of **1c** in the presence of Cu(I)/**L4**, followed by the one-pot reduction/oxidation carried out with BH_3·THF and $NaOH/H_2O_2$, respectively. After oxidation, the analysis of the product revealed complete conversion, excellent enantiomeric excess (> 99% *e.e.*) and high diastereomeric purity (*syn:anti* ratio = 91:9). The enantiomerically and diastereomerically pure product could be isolated in excellent yield (90%, Table 3.3, entry 4). In order to obtain the corresponding *anti*-diastereoisomer, the chiral β-boryl imine **5c**, obtained in the presence of Cu(I)/**L4** was reduced with $NaBH_4$ in

MeOH. The *anti*-diastereoisomer was formed with excellent enantioselectivity (>99% *e.e.*), sufficiently high diastereoselectivity (*syn:anti* ratio = 17:83), and the pure *anti*-product could be isolated in good yield (67%). The β-borations of (*E*)-*N*-(4-phenylbut-3-en-2-ylidene)aniline (**1d**) and (*E*)-N-(4-phenylbut-3-en-2-ylidene)butan-1-amine (**1b**) were followed by one pot reductions/oxidations of the enantioenriched β-boryl imines **5d** and **5b**, using the reducing agents BH_3·THF and DIBAL-H, respectively, to guarantee high diastereoselectivities in the formation of the *syn*-diastereoisomers. In all cases the *syn:anti* ratio was over 99:1 (Table 3.3, entries 12-21, and Table 3.4, entries 1-10) in agreement with the observations made in the course of the optimization of the reduction method (Table 3.1 and 3.2). The high enantioselectivities obtained with the Cu/phosphoramidite (**L9**) for **5d**, and with Cu/Taniaphos (**L2**) for **5b**, combined with the excellent diastereoselectivities provided by the reducing agents BH_3·THF and DIBAL-H, respectively, allowed us to isolate the pure *syn*-diastereoisomers of **9d** and **9b** in 69% and 92% isolated yields (Table 3.3, entry 20 and Table 3.4, entry 2).

In summary, we have succeeded in optimizing the copper-catalyzed asymmetric β–boration/reduction/oxidation of three imines derivatives of benzylideneacetone obtaining high or total control of the enantiomeric- and diastereomeric purity of the targeted γ–amino alcohols (Scheme 3.11).

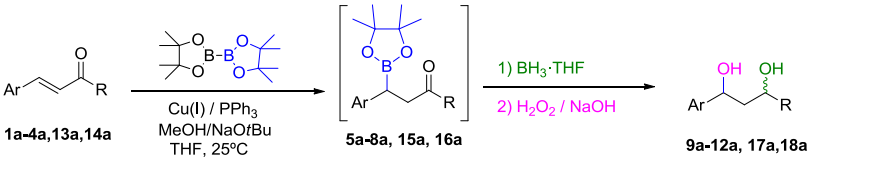


Scheme 3.11. Synthesis of the enantioenriched *syn*- and *anti*-γ-amino alcohols from 1-phenyl-N-(4-phenylbut-3-en-2-ylidene)methanamine *via* a one-pot β–boration/reduction/oxidation process.

3.4 Comparative study on the one-pot approach applied to a range of α,β–unsaturated imines and ketones

Considering the importance of chiral γ–amino alcohols in pharmaceutical applications [15] and their notable role as chiral synthons, [16] chiral auxiliaries [17] and chiral ligands in transition metal catalysis, [18] we decided to survey the possibility of extending the range of α,β–unsaturated imines employed, as well as comparing this study with the analogous transformations of the corresponding α,β–unsaturated ketones into chiral 1,3-diols.

The stereoselectivity of the β-boration / reduction / oxidation process is determined by two independent factors, that is, the enantioselectivity of the boron conjugate addition reaction, and the diastereoselectivity of the stoichiometric reduction of the C=N or C=O double bond. In the previous section, we exhaustively studied these two issues in the case of three α,β–unsaturated imines. Although principally the reaction sequence can be applied to the transformation of the corresponding α,β-unsaturated ketones, we were aware that these substrate might show completely different behaviour under the reaction conditions. For this reason, we decided to carry out the β–boration of α,β–unsaturated ketones using achiral Cu(I) catalysts, and the racemic organoboranes were converted *in situ* into the corresponding products *via* stoichiometric reduction of the carbon-oxygen double bond, followed by oxidative substitution of the C-Bpin moiety (Scheme 3.12).



1a: Ar= Ph, R= Me
2a: Ar= p-MeO-C_6H_4, R= Me
3a: Ar= p-Cl-C_6H_4, R= Me
4a: Ar= Ph, R= Ph
13a: 2-cyclohexen-1-one
14a: trans-3-nonen-2-one

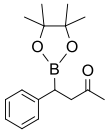
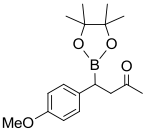
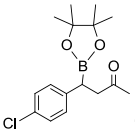
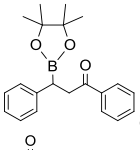
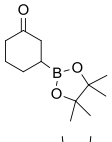
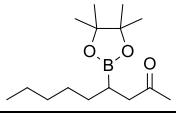
5a: Ar= Ph, R= Me
6a: Ar= p-MeO-C_6H_4, R= Me
7a: Ar= p-Cl-C_6H_4, R= Me
8a: Ar= Ph, R= Ph
15a: β-boryl cyclohexenone
16a: β-boryl 3-nonen-2-one

9a: Ar= Ph, R= Me
10a: Ar= p-MeO-C_6H_4, R= Me
11a: Ar= p-Cl-C_6H_4, R= Me
12a: Ar= Ph, R= Ph
17a: 2,4-cyclohexanediol
18a: 2,4-nonanediol

Scheme 3.12. Synthesis of 1,3-diols from α,β-unsaturated ketones *via* a one-pot catalytic β-boration / reduction / oxidation process.

The $CuCl/PPh_3$ catalyst system efficiently β-borated the α,β-unsaturated ketones into the organoboronate intermediates **5a**-**8a, 15a, 16a**, in the presence of 1.1 equivalents of bis(pinacolato)diboron (B_2pin_2) at room temperature (Table 3.5). The addition of base (NaO*t*Bu) was crucial for the quantitative transformation of the substrates into the desired products.

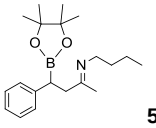
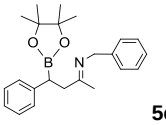
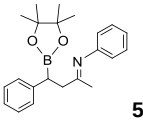
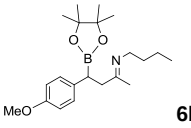
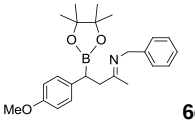
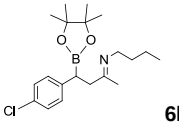
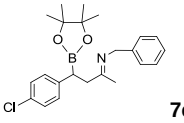
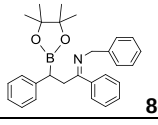
Table 3.5. $CuCl/PPh_3$ catalysed β-boration of α,β-unsaturated ketones [a].

Entry	Organoborane	Conv. (%)[b]	Isolated yield(%)	$^{11}B\{^1H\}$-NMR (ppm)
1	 **5a**	99	42	37.0
2	 **6a**	90	82	33.6
3	 **7a**	98	91	33.1
4	 **8a**	99[c]	57	34.1
5	 **15a**	100	88	33.4
6	 **16a**	100	52	38.1

[a] Standard conditions for the β-boration : 0.25 mmol substrate, 2 mol% CuCl, 4 mol% PPh_3, 1.1 eq. B_2pin_2, 3 mol% NaO*t*Bu, 2 eq. MeOH, THF (2.5 mL), rt, 6h; [b] Conversion calculated by ^1H NMR spectroscopy. [c] 12h.

Importantly, the ^{11}B chemical shifts of the β–boryl ketones and the corresponding β–boryl imines differ significantly (Table 3.5 and 3.6). While the chemical shift of β-boryl ketones falls in the range of 33.0-37.0 ppm (Table 3.5), the boron signals of the corresponding β-boryl imines appear between 18.1-21.7 ppm (Table 3.6).

Table 3.6. $CuCl/PPh_3$ catalysed β-boration of α,β-unsaturated imines [a].

Entry	Organoborane	Conv. (%)[b]	Isolated yield(%)	$^{11}B\{^1H\}$-NMR (ppm)
1	 **5b**	99	70	21.7
2	 **5c**	99	82	21.1
3	 **5d**	40	29	21.4
4	 **6b**	99	97	20.2
5	 **6c**	99	85	19.2
6	 **6b**	99	89	19.0
7	 **7c**	99	85	18.9
8	 **8c**	99[c]	78	18.1

[a] Standard conditions for the β-boration : 0.25 mmol substrate, 2 mol% CuCl, 4 mol% PPh_3, 1.1 eq. B_2pin_2, 3 mol% NaO*t*Bu, 2 eq. MeOH, THF (2.5 mL), rt, 6h; [b] Conversion calculated by ^1H NMR spectroscopy; [c] 12h.

The shift to higher fields of the boron signals in β-boryl imines is diagnostic of the intramolecular interaction between N and B. [19] For the analogous β-boryl ketones, there is no evidence of any intramolecular B-O interaction in the solution phase, which is line with the lack of such interaction in the solid phase confirmed by the X-ray structures of organoboranes **5a** and **8a** (Figures 3.7 and 3.8).

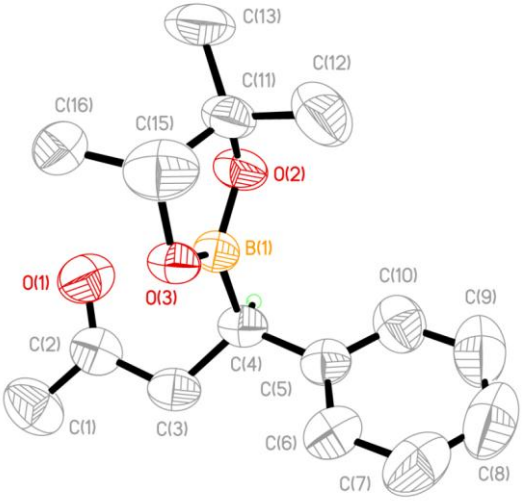


Figure 3.7 Molecular diagram of β-boryl imine **5a**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity except H(4). Selected bond lengths (Å) and angles (º): B(1)-O(1) 2.706, O(1)-C(2) 1.204(2), B(1)-O(3) 1.3580(18), B(1)-O(2) 1.3594(18), B(1)-C(4) 1.567(2), C(1)-C(2) 1.493(3), C(2)-C(3) 1.493(2), C(3)-C(4) 1.517(2), O(3)-B(1)-O(2) 113.37(13), O(2)-B(1)-C(4) 123.21(13), O(1)-C(2)-C(3) 121.31(15).

The B(1)-O(1) distance in compound **5a** is 2.706 Å, much higher than the sum of the covalent radii of boron and oxygen, indicating negligible interaction between the boron and oxygen centres. The same situation is observed in the case of compound **8a** where the B(1)-O(1) distance is 2.854 Å, *i.e.* even higher than in compound **5a**.

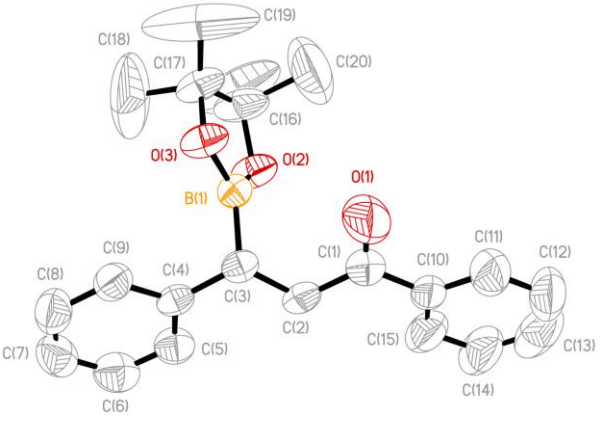
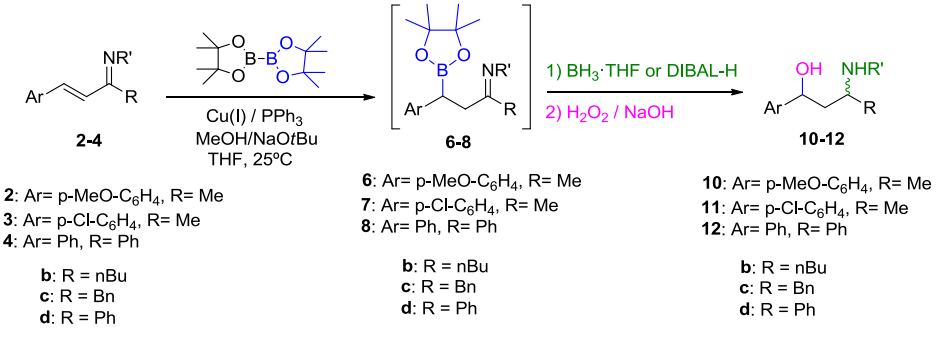


Figure 3.8. Molecular diagram of β-boryl imine **8a**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (º): B(1)-O(1) 2.854, O(1)-C(2) 1.206(6), B(1)-O(3) 1.354(5), B(1)-O(2) 1.357(5), B(1)-C(3) 1.565(6), C(1)-C(2) 1.491(7), C(2)-C(3) 1.518(6), C(3)-C(4) 1.521(6), O(3 B(1 O(2 112.8(3), O(1)-C(1)-C(10) 120.3(5), O(2)-B(1)-C(3) 122.3(4), C(1)-C(2)-C(3) 112.9(4), C(4)-C(5)-C(6) 120.6(5).

For the reduction of C=N bond, we have worked with three β–boryl imines **6, 7** and **8** (obtained from β–boration of **2, 3** and **4**, respectively) to extend the substrate scope and to identify those structural features of the substrates which mostly influence the diastereoselectivity in the reduction / oxidation of organoboranes (Scheme 3.13).



2: Ar= p-MeO-C_6H_4, R= Me
3: Ar= p-Cl-C_6H_4, R= Me
4: Ar= Ph, R= Ph

b: R = nBu
c: R = Bn
d: R = Ph

6: Ar= p-MeO-C_6H_4, R= Me
7: Ar= p-Cl-C_6H_4, R= Me
8: Ar= Ph, R= Ph

b: R = nBu
c: R = Bn
d: R = Ph

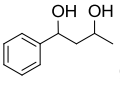
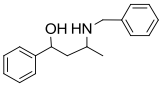
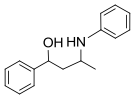
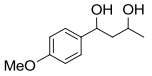
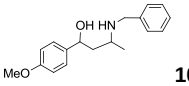
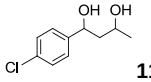
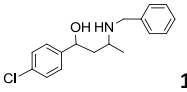
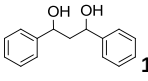
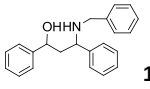
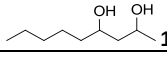
10: Ar= p-MeO-C_6H_4, R= Me
11: Ar= p-Cl-C_6H_4, R= Me
12: Ar= Ph, R= Ph

b: R = nBu
c: R = Bn
d: R = Ph

Scheme 3.13. Synthesis of 1,3-amino alcohols from α,β-unsaturated imines *via* a one-pot catalytic β-boration / reduction / oxidation process.

The diastereoselectivity of the reactions was determined by ^{1}H-NMR studies on the crude and isolated 1,3-diols (**9a**, **10a**, **11a**, **12a**, **17a** and **18a**) and 1,3-amino alcohols (**9b-d**, **10b-c**, **11b-c**, **12c**). We found that in most cases, the stoichiometric reduction / oxidation of organoborane intermediates indeed takes place with good to excellent *syn*-selectivity (Table 3.7).

Table 3.7 Diastereoselective reduction / oxidation of β-boryl ketones and β-boryl imines with BH_3·THF and H_2O_2/NaOH [a].

Entry	Difunctionalized product [b]	*Syn/anti* ratio	Isolated yield (%)	*Syn/anti* ratio of the isolated product
1	 **9a**	95/5	85	99/1
2	 **9c**	95/5	82	99/1
3	 **9d**	99/1	95	99/1
4	 **10a**	83/17	71	99/1
5	 **10c**	77/23	80	98/2
6	 **11a**	86/14	82	99/1
7	 **11c**	87/13	73	98/2
8	 **12a**	99/1	95	99/1
9	 **12c**	99/1	90	99/1
10	 **17a**	30/70	60	1/99
11	 **18a**	80/20	63	99/1

[a] Standard conditions for the reduction: β-boryl ketone or imine (0.5 mmol), BH_3·THF (1M) (1.5 mL, 1.5 mmol), THF (2 mL), 0ºC to 25ºC, 15h. Standard conditions for the oxidation: NaOH (aq.) (10 mL of 1.0M solution, 10 mmol) and H_2O_2 (aq.) (750ml of 30% v/v solution, 7.6 mmol, rt, 3h. [b] Conversion calculated by ^{1}H NMR spectroscopy were >99% in all the examples, in at least two reproducible reactions.

It is worth mentioning that apart from the ^{1}H-NMR evidence, the formation of the *syn*-products was also confirmed by X-ray studies on **12a** (Figure 3.9).

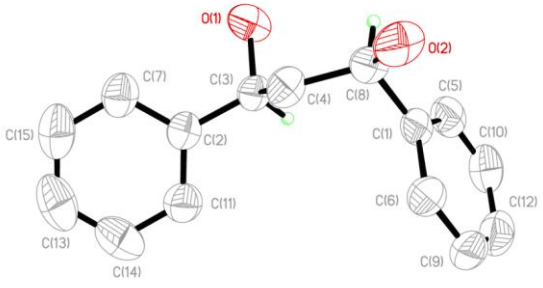
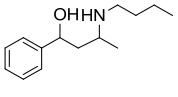
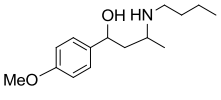
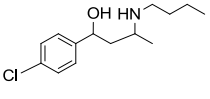


Figure 3.9. Molecular diagram of 1,3-diol **12a**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity except H(3) and H(8). Selected bond lengths (Å) and angles (º): O(1)-C(3) 1.432(3), C(1)-C(8) 1.516(3), O(2)-C(8) 1.434(3), C(2)-C(3) 1.512(3), C(3)-C(4) 1.522(4), C(4)-C(8) 1.524(3), O(1)-C(3) 1.432(3), O(1)-C(3)-C(2) 111.66(19), C(2)-C(3)-C(4) 113.14(19), C(2)-C(3)-C(4) 113.14(19).

Notable exceptions are the reduction / oxidation of β-boryl *n*-butylimines which afforded the corresponding 1,3-amino alcohols without considerable stereodifferentiation between the *syn*- and *anti*-diastereoisomers (Table 3.8).

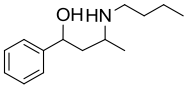
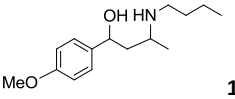
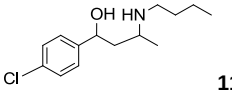
Table 3.8 Diastereoselective reduction / oxidation β-boryl phenylimine with BH_3·THF and H_2O_2 / NaOH [a].

Entry	Difunctionalized product	Conv [b] (%)	*Syn/anti* ratio
1	 **9b**	99	53/47
2	 **10b**	99	54/46
3	 **11b**	99	60/40

[a] Standard conditions for the reduction: β-boryl ketone or imine (0.5 mmol), BH_3·THF (1M) (1.5 mL, 1.5 mmol), THF (2 mL), 0ºC to 25ºC, 15h. Standard conditions for the oxidation: NaOH (aq.) (10 mL of 1.0M solution, 10 mmol) and H_2O_2 (aq.) (750ml of 30% v/v solution, 7.6 mmol, rt, 3h. [b] Conversion calculated by ^{1}H NMR spectroscopy were >99% in all the examples, in at least two reproducible reactions.

In order to improve the diastereoselectivity of the *syn*-1,3-amino alcohol, we turned our attention to the alternative reducing reagent, DIBAL-H·THF, which provided high *syn*-diastereoselection on the β-boryl n-butylimine (Table 3.9, entry 1). When the β-boryl-n-butylimines **6b** and **7b** were reduced and oxidized with DIBAL-H in THF and H_2O_2/NaOH respectively, the formation of the *syn*- *versus* the *anti*-diastereoisomer increased, although no exclusive formation of either the *syn*-**10b** and *syn*-**11b** products could be achieved. Contrary to the case of acyclic susbtrates, the reduction / oxidation of 3-boryl-cyclohexen-1-one (**15a**) with BH_3·THF and H_2O_2/NaOH, gave the *anti*-diastereoisomer **17a** as the major product (Table 3.7, entry 10).

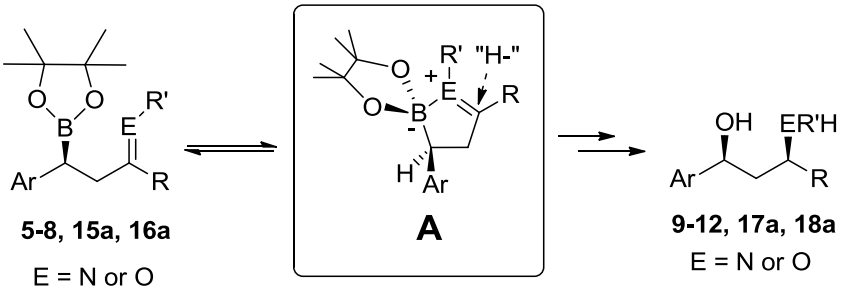
Table 3.9. Diastereoselective reduction / oxidation of β-boryl n-butylimines with DIBAL-H·THF and H_2O_2/NaOH [a].

Entry	Difunctionalized product	Conv. (%)[b]	*Syn/anti*	Isolated yield(%)	*Syn/anti* of pure product
1	 **9b**	90	99/1	84	99/1
2	 **10b**	99	77/23	47	99/1
3	 **11b**	99	82/18	52	99/1

[a] Standard conditions for the reduction: β-boryl n-butylimines (0.5 mmol), DIBAL-H-THF (3 eq), THF (2 mL), -78ºC to 25ºC, 15h. Standard conditions for the oxidation: NaOH (aq.) (10 mL of 1.0M solution, 10 mmol) and H_2O_2 (aq.) (750ml of 30% v/v solution, 7.6 mmol, rt, 3h. [b] Conversion calculated by ^{1}H NMR spectroscopy.

To explain the pronounced *syn*-selectivity of the reaction sequence (Scheme 3.12 and 3.13), we suggest a model based on the close proximity of the Lewis acidic boryl group and the Lewis basic ketone / imine functionality in the organoborane intermediates **5-8, 15a** and **16a**. If we consider an intramolecular Lewis acid-Lewis base interaction between the two functional groups (*i.e.* **A**, Scheme 3.14), the cyclic B-N chelate structures formed upon such an interaction have two sterically

different diastereotopic faces. The primary factor that creates the facial differentiation is the substituent on the β-carbon, as shown in Scheme 3.14. Other steric features of the molecules (such as the large boronate ester group) are expected to exert a similar steric influence on both sides of the C=N or C=O functionality, however, they could contribute by amplifying or reducing the effect of the β-substituent. It is important to note that the existence of such interactions are widely accepted in the literature, [10,20] even in the case of ketones and aldehydes, [21] however, to the best of our knowledge and in line with our findings, direct spectroscopical evidence has never been presented.

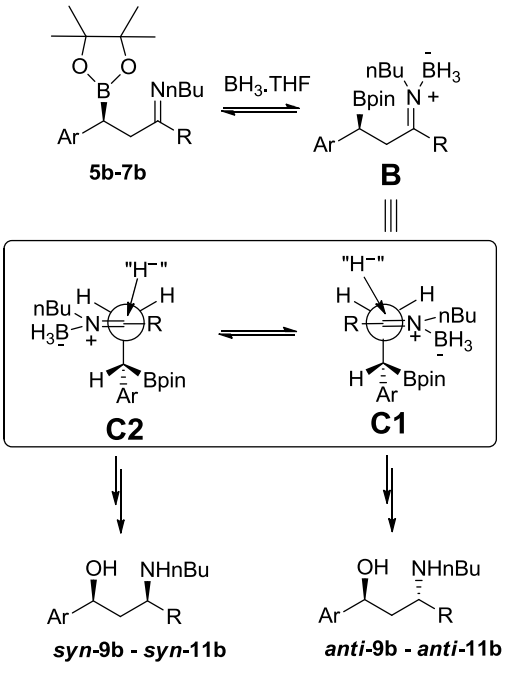


Scheme 3.14 Presumed intramolecular Lewis-type acid-base interaction in organoboronates **5-8, 15a** and **16a** resulting in the formation of the *syn*-diastereoisomers **9**-**12, 17a** and **18a**.

For this reason, we have made a considerable effort to find structural and spectroscopic evidence for the internal Lewis acid-Lewis base interaction shown schematically in Scheme 3.14 by structure **A**. Despite the lack of solid-state structural evidence, there is a clear spectroscopic indication of intramolecular B-N interaction as shown in Table 3.6. The observed $\Delta\delta$ between the $^{11}B\{^{1}H\}$-NMR chemical shifts of the β-boryl ketones and the corresponding β-boryl imines are consistent with partial rehybridization of the B atom from pure sp^2 towards sp^3 in the case of the β-boryl imines upon the formation of the intramolecular Lewis adducts. Presumably the controling element in the formal hydride addition that results in high *syn*-diastereocontrol is indeed a complex of type **A** (Scheme 3.14). In the case of ketones, the explanation forwarded by previous workers in this area,

seems to be a sound hypothesis since such complexes can effect remote asymmetric induction processes. [20]

In contrast to the highly *syn*-diastereocontrolled reduction reaction, the origin of the dominant *anti*-selectivity in the reduction / oxidation of 3-boryl-cyclohexen-1-one (**15a**), can be explained by the lack of intramolecular Lewis acid-Lewis base interactions between the B and O centres, due to the cyclic conformational restrictions of the molecule. As expected with 3-substituted cyclohexanones, hydride reduction occurs to give predominantly 1,3-*anti*-stereocontrol, as explained elsewhere. [22] However, the origin of the reduced *syn*-diastereocontrol upon formation of the *N*-n-butyl amino alcohols **9-11b** (see Scheme 3.15) is less clear. In these cases, the *syn*-diastereocontrol remains in place to some extent, perhaps *via* the intramolecular B-N complex **5b**-**7b**, as outlined in Scheme 3.14. However, a more likely explanation is that in the presence of BH_3-THF, there is the competing effect of intermolecular N-B complexation with the reducing agent BH_3-THF due to the more electron rich *n*-butyl imine (see Scheme 3.15). This would have the effect of allowing acylic stereoselection processes to occur, which are likely to be governed by the types of effects used to explain additions to chiral ketone systems. [23] Hence, *n*-butyl-BH_3 activated complexes of type **B** could undergo additions as outlined in Scheme 3.15 to derive both *syn*- and *anti*-products *via* reactive conformations **C1** and **C2**. In these types of models, we predict that Ar behaves as the larger group leaving the Bpin moiety to stabilize or destabilise either of the possible reactive conformations. In fact, there may be little to choose between confomations **C1** and **C2**, with **C1** having possible stereoelectronic repulsion between the electropositive formal imminium ion, and **C2** having steric repulsion between the R-group and Bpin. The net result would be approximately equal amounts of both the *syn*- and *anti*-diastereoisomers being formed, as is indeed observed.



Scheme 3.15 Proposed origin of the competing *anti*-diastereoselection in the BH_3-mediated reduction to derive amino alcohols **9-11b.**

The overall stereoselectivity of the β-boration / reduction / oxidation reaction was next addressed through the enantioselective β-boration of the α,β-unsaturated ketones **1a-4a**, **13a** and **14a** and the corresponding α,β-unsaturated imines. The substrates were β–borated using copper(I) complexes modified with chiral bidentate ligands, and the boron conjugate additions were followed by the in *situ* reduction and oxidation with the appropriate reducing reagent (BH_3·THF or DIBAL-H·THF) and H_2O_2/NaOH. Yun and coworkers reported moderate to high enantioselectivities for the copper β–boration of α,β–unsaturated ketones using Josiphos and Mandyphos type ligands. [13] Moreover, we have just described that this type of diphosphine can induce excellent enantioselectivities for the β–boration of α,β–unsaturated imines and this enantioselectivity is conserved during the reduction/oxidation steps. With this information in mind, the chiral ligands

explored were Josiphos diphosphines (**L4,L11**) and Mandyphos diphosphines (**L12, L13**) (Figure 3.10).

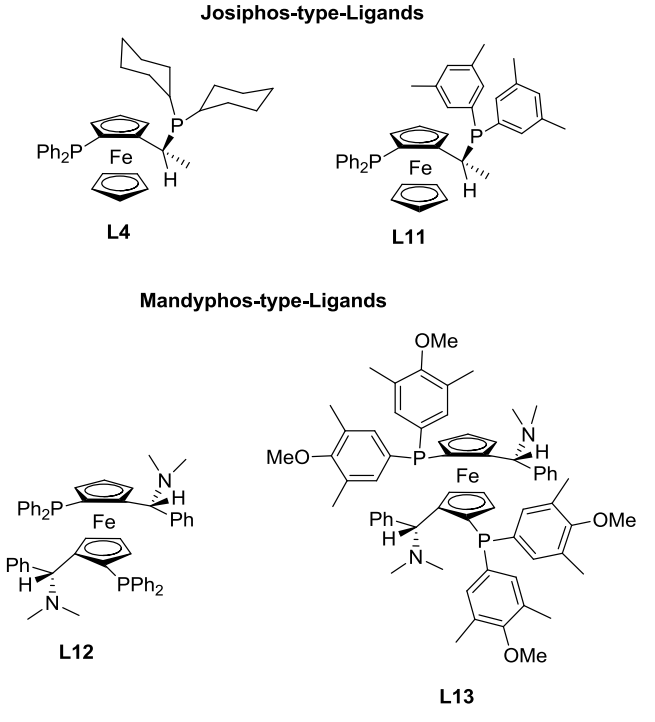
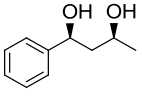
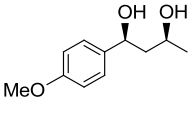
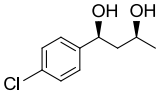
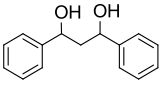


Figure 3.10 Structures of the chiral ligands using for the β–boration of α,β–unsaturated ketones and imines following for in *situ* reduction/oxidation.

The enantiomeric excess of **1a** was variable, ranging from 8% with the catalytic system CuCl/ligand **L4** to 75% with CuCl/ligand **L12** (Table 3.10, entries 1-4). The asymmetric induction observed is in agreement with related reports. [13] Ligand **L11** and the two Mandiphos type ligands **L12** and **L13** provided decent enantioselectivities in the asymmetric β-boration of the analogous substrates **2a** and **3a**, while the chiral ligand **L4** was quite inefficient with *e.e.* <10% (Table 3.10, entries 5-12). Neither the electron donating nor the electron releasing substituents on the phenyl group in the β-position of the substrate had a relevant influence on the asymmetric β-boration.

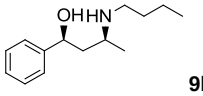
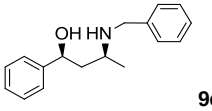
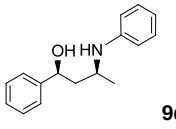
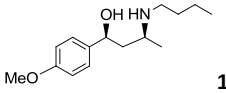
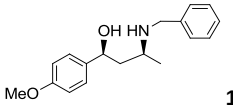
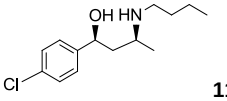
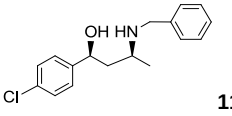
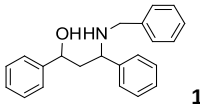
Table 3.10 Enantio- and diastereo-selective β-boration / reduction / oxidation of α,β-unsaturated ketones with Cu-chiral ligands [a].

Entry	Product	Chiral Ligand	Conv. (%)[b]	*Syn/anti*	*e.e.* (%)[c]
1	 **9a**	**L4**	99	92/8	8
2	"	**L11**	99	90/10	66
3	"	**L12**	99	95/5	75
4	"	**L13**	99	90/10	52
5	 **10a**	**L4**	99	83/17	3
6	"	**L11**	99	82/18	65
7	"	**L12**	44	83/17	10
8	"	**L13**	71	83/17	42
9	 **11a**	**L4**	99	88/12	5
10	"	**L11**	99	84/16	42
11	"	**L12**	90	86/14	61
12	"	**L13**	96	84/16	65
13[d]	 **12a**	**L4**	99	99/1	2
14[d]	"	**L11**	99	99/1	42
15[d]	"	**L12**	99	99/1	73
16[d]	"	**L13**	90	99/1	84

[a] Standard conditions for the β-boration : 0.25 mmol substrate, 2 mol% CuCl, 4 mol% PPh_3, 1.1 eq. B_2pin_2, 3 mol% NaO*t*Bu, 2 eq. MeOH, THF (2.5 mL), rt, 6h. Standard conditions for the reduction: β-boryl ketone (0.5 mmol), BH_3·THF (1M) (1.5 mL, 1.5 mmol), THF (2 mL), 0ºC-25ºC, 15h. Standard conditions for the oxidation: NaOH (aq.) (10 mL of 1.0M solution, 10 mmol) and H_2O_2 (aq.) (750ml of 30% v/v solution, 7.6 mmol, rt, 3h. [b] Calculated by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis. [d] 12h.

However, it is worth mentioning that in the case of the corresponding α,β-unsaturated imines, the CuCl / ligand **L4** catalytic system provided the best results (Table 3.11).

Table 3.11 Enantio- and diastereo-selective β-boration / reduction / oxidation of α,β-unsaturated imines with Cu-chiral ligands [a].

Entry	Product	Chiral Ligand	Conv. (%)[b]	*Syn/anti*	*e.e.* (%) [c]
1[d]	 **9b**	**L4**	94	99/1	80
2	 **9c**	**L4**	99	91/9	99
3	 **9d**	**L4**	99	99/1	52
4[d]	 **10b**	**L4**	99	54/46	79
5	 **10c**	**L4**	99	71/29	93
6[c]	 **11b**	**L4**	99	57/43	56
7	 **11c**	**L4**	99	82/18	61
10[e]	 **12c**	**L4**	99	99/1	65

[a] β-boration : 0.25 mmol substrate, 2 mol% CuCl, 4 mol% PPh_3, 1.1 eq. B_2pin_2, 3 mol% NaO*t*Bu, 2 eq. MeOH, THF (2.5 mL), rt, 6h. Reduction: β-boryl imine (0.5 mmol), BH_3·THF (1M) (1.5 mL, 1.5 mmol), THF (2 mL), 0ºC-25ºC, 15h. Standard conditions for the oxidation: NaOH (aq.) (10 mL of 1.0M solution, 10 mmol) and H_2O_2 (aq.) (750ml of 30% v/v solution, 7.6 mmol, rt, 3h. [b] Calculated by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis. [d] Reduction: β-boryl n-butylimines (0.5 mmol), DIBAL-H-THF (3 eq), THF (2 mL), -78ºC to 25ºC, 15h; [e] 12h.

Electron rich substrates could be transformed into the corresponding γ-aminoalcohols with *e.e.* values between 93 and 99%, (Table 3.11, entries 2 and 5). Substituents on the N atom of the imines had an influence on the enantioselectivity of the β-boration, as can be seen in Table 3.11 and Figure 3.11. The electronic and steric properties of the imino benzyl group also had a beneficial effect on the enantioselectivity of the asymmetric β-boration.

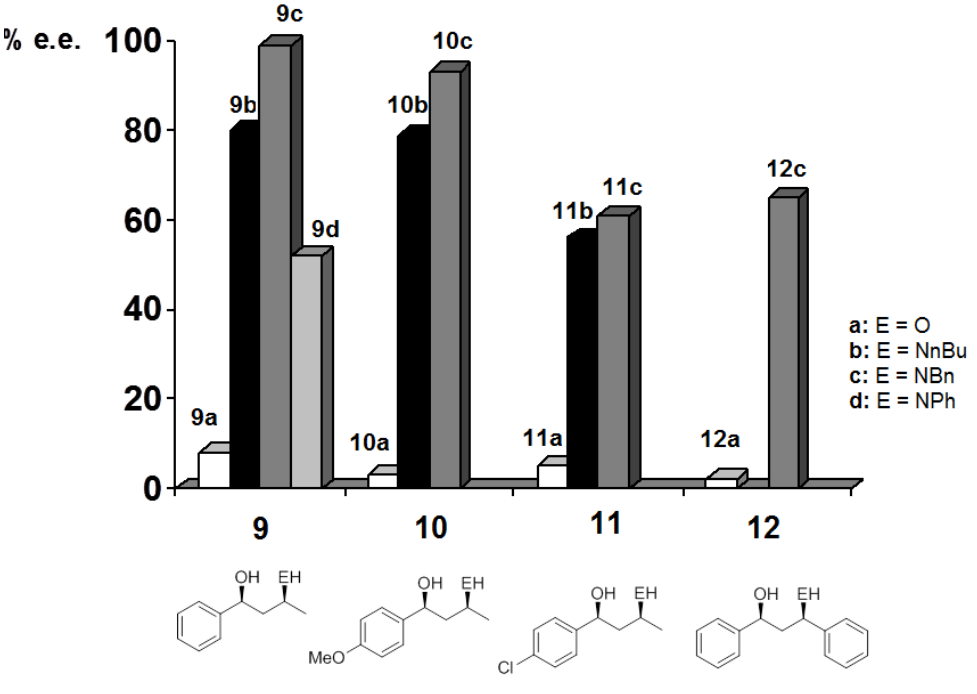


Figure 3.11. Relative values of enantiomeric excesses on the catalytic β-boration / reduction / oxidation of α,β-unsaturated ketones and imines using CuCL/Josiphos chiral ligand **L4**.

The benefits of our methodology with respect to the reported methodologies is based on the use of simple, achiral, α,β-unsaturated ketones or imines and the use of non-expensive copper catalyst for the β-boration. The asymmetric β-boration is achieved by the use of catalytic amounts of copper(I) complexes modified with chiral diphosphines, and the reduction / oxidation procedure can be performed with appropriate reducing agents to obtain the *syn*-diastereoisomer with

high selectivity, and retaining the configuration at the β–carbon, in a one-pot sequence.

3.5 Novel 4, 5-step one-pot sequence to synthesize γ–amino alcohols, 1,3-oxazine respectively

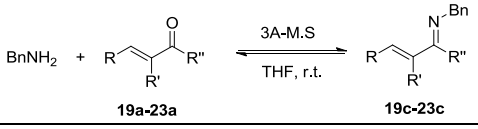
In the previous section we demonstrated a novel highly enantio- and diastereo-selective route to γ-amino alcohols **9b,c,d – 12b,c,d** *via* a three-step protocol involving stable, isolable α,β-unsaturated imines that have in common a Ph substituent in the β–position. It was demonstrated that asymmetric β-boration of these α,β-unsaturated imines resulted in β-boryl imine species **5b,c,d – 8b,c,d**, which could undergo substrate-controlled asymmetric C=N reduction and C-B oxidation to give γ-amino alcohols **9b,c,d – 12b,c,d** in good yields.

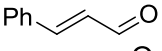
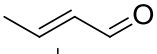
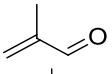
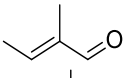
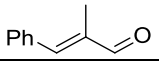
Although this was a powerful methodology for the synthesis of γ-amino alcohols, the general application of this methodology was severely limited by the range of α,β-unsaturated imines **1b,c,d – 4b,c,d** that could be isolated. Normally imines are prepared by condensation of amines with the corresponding aldehydes or ketones, however, in the case of α,β–unsaturated carbonyl compounds the competitive 1,4-addition of the amine diminishes the C=N formation and hence the methodology was only applicable for stable, chalcone derived-imines.

The synthesis of α,β-unsaturated imines is surprisingly underexplored compared to the corresponding imine formation from non-conjugated aldehydes or ketones, [24] though the synthesis of substituted dihydropyridines and pyridines from certain less-substituted α,β-unsaturated imines [25] has been reported. We therefore investigated the potential formation of a range of less-substituted α,β-unsaturated imines by *in situ* IR spectroscopy (ReactIR), [26] to gain insight into the relative rates and selectivity of α,β-unsaturated imine **19-23** formation vs. Michael addition, as outlined in Table 3.12. This experiment was performed by the team of Prof. Whiting at Durham University and proved to be an ideal tool for monitoring this reaction (see Table 3.12) for both selectivity and rate. Formation of

the imines was complete within 6h under these mild conditions.

Table 3.12 Monitoring the imine formation α,β–unsaturated aldehydes using ReactIR carried out at Durham University by the team of Prof. Whiting.



Entry	Substrate	α,β-unsaturated imine [a,b]	Time (min) [c]
1		**19c**	15
2		**20c**	50
3		**21c**	90
4		**22c**	100
5		**23c**	360

[a] 1,2- *vs.* 1,4-Addition. [b] Conditions: THF (7 mL), 3Å molecular sieves (2.5 g), aldehyde (2.8 mmol) and $BnNH_2$ (2.8 mmol) stirred in open-air. [c] Time required for reaction completion.

Facile imine formation of **21** is exemplified by Figure 3.12, showing loss of the C=O stretch (1698 cm^{-1}) and concomitant gain of the C=N (*asym* + *sym*) stretches (1640 & 1621 cm^{-1} respectively).

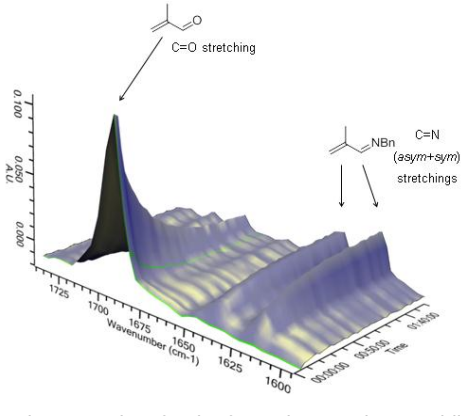
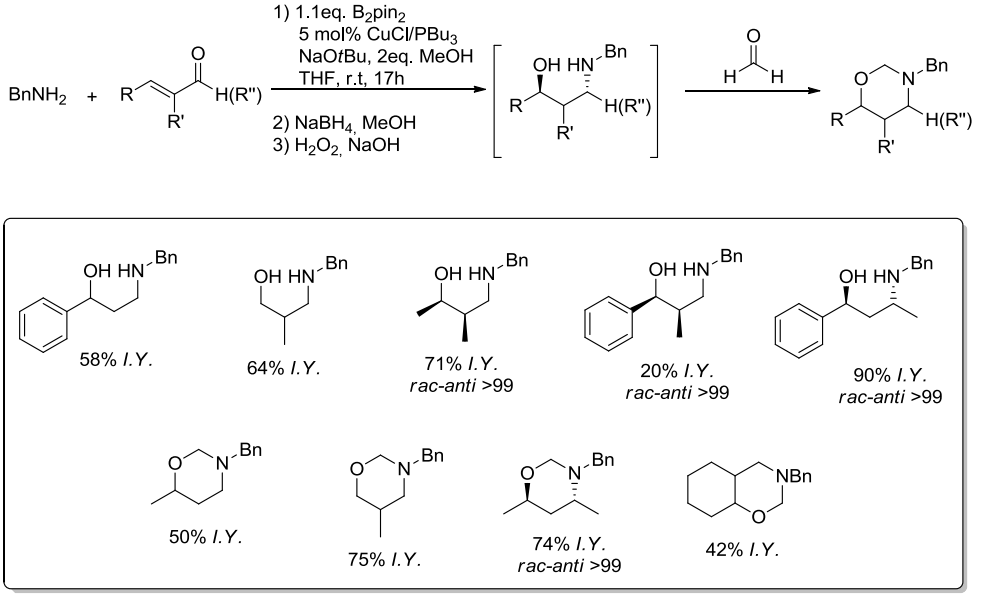


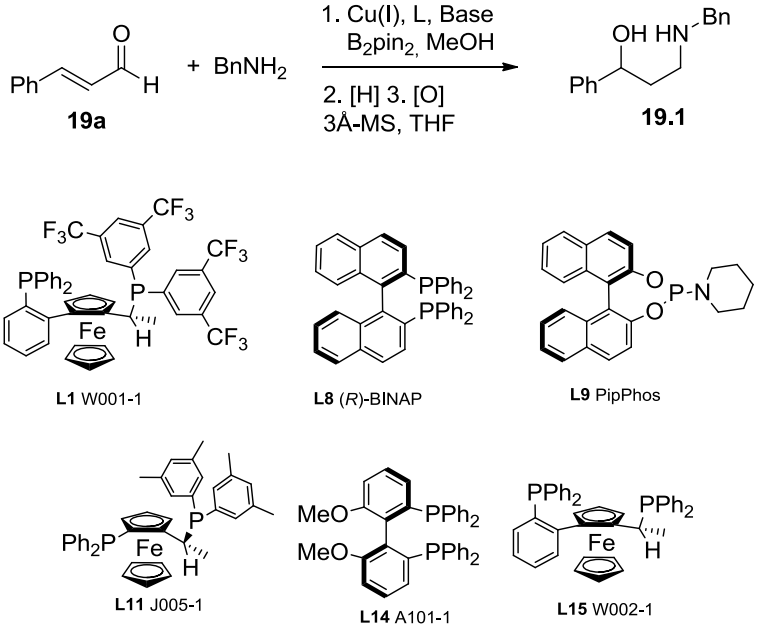
Figure 3.12 ReactIR plots over time for the formation **21** *via* 1,2-addition of benzylamine to methacrolein. Experiment carried out at Durham University by the team of Prof. Whiting.

With this knowledge in hand, the team of Prof. Whiting (Durham University) developed a four-step, one-pot methodology for the synthesis of the desired β–amino alcohols. To illustrate the successful approach the Scheme 3.16 shows the most relevant γ–amino alcohols formed following this one-pot sequential transformation. With addition of formaldehyde, the corresponding 1,3-oxazine was also isolated in a one-pot, five-step sequence.



Scheme 3.16. More general transformation of α,β–unsaturated aldehydes and ketones into γ–amino alcohols or 1,3-oxazines *via* one-pot sequence (carried out by the team of Prof. Whiting at Durham University).

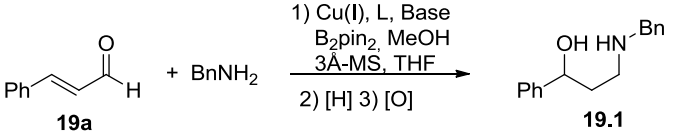
The asymmetric potential of this efficient 4-step (or 5), one-pot methodology was also investigated by our group, using **19a** as substrate and $BnNH_2$ in the presence of a copper-catalyst and different chiral diphosphine, such as **L1**, **L8-9**, **L11**, **L14-15** (Scheme 3.17).



Scheme 3.17 Asymmetric approach of the β–boration of the imine formed *in situ* from cinnamaldehyde **19a** followed by reduction/oxidation steps.

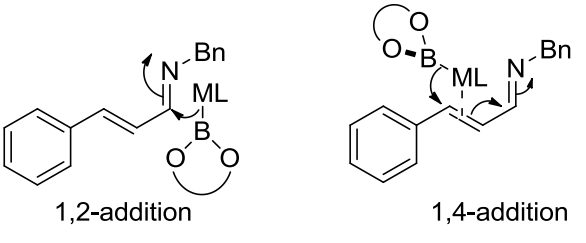
The cinnamaldehyde **19a** can sufficiently be converted into the γ-amino alcohol in high conversion (83%) when PPh_3 is employed as the ligand (Table 3.13, entry 1). However, the use of chiral phosphines decreases significantly the conversions (12-31%). Moreover, the enantiomeric excess on the γ–amino alcohol **19.1** was very low (5-11% *ee.*). The former result can be rationalized by the competitive 1,2- vs 1,4-addition of M-Bpin to the substrate (Scheme 3.18). [27]

Table 3.13 Ligand screening in the β-boration of the imine formed *in situ* from cinnamaldehyde [a].



Entry	L (mol%)	Conv. (%)[b]	*e.e.* (%) [c]
1	PPh_3 (6)	83	-
2	**L13** (3)	26	0
3	**L8** (3)	14	11
4	**L4** (3)	31	0
5	**L9** (3)	14	7
6	**L10** (3)	22	5
7	**L16** (6)	12	0

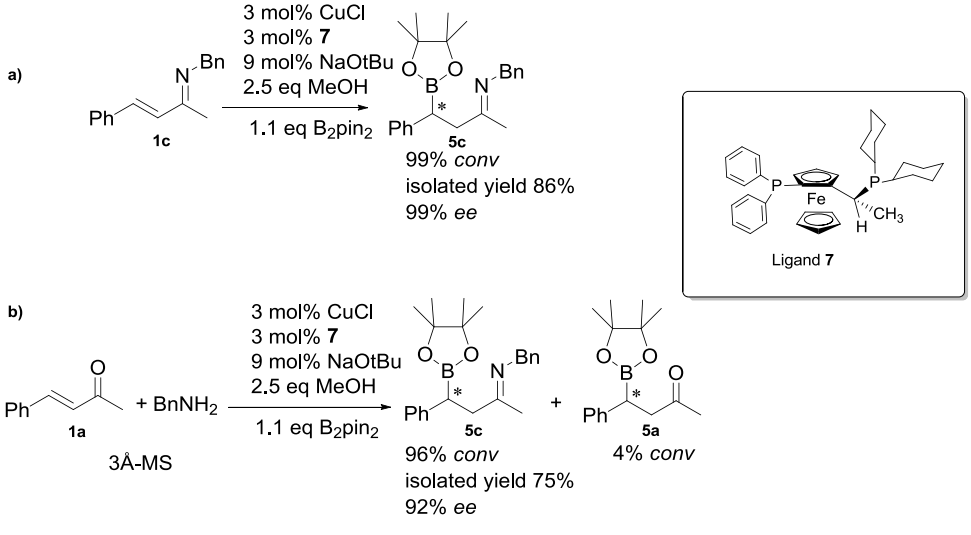
[a] Standard conditions: 0.25 mmol cinnamaldehyde, 0.25 mmol benzylamine, CuCl (3%), **L** (3-6%), NaO*t*Bu (20%), 3Å-M.S. (250 mg), MeOH (2.5 equiv.) and THF (1.3 mL), 16h, 25ºC.Reduction conditions: $NaBH_4$ (3 equiv.) and MeOH (0.5 mL) 3h; Oxidation conditions: H_2O_2 (3 equiv.) and NaOH (3 equiv.). [b] Determined by ^{1}H-NMR spectroscopy. [c] Determined by chiral HPLC-UV.



Scheme 3.18 Competitive 1,2- and 1,4-boration addition to the imine of cinnamaldehyde **19a**.

The substrate α,β–unsaturated ketone **1a** was able to be transformed into the imine **5c** form. We have already discussed the efficient formation of the desired β-boryl imine **5c** up to 92% *e.e*. Importantly, when the reaction was carried out following a one-pot, 4 steps, protocol, the asymmetric induction was almost identical to that obtained when the enantioselective β-boration took place from the isolated the α,β-unsaturated imine (Scheme 3.19). It is interesting to note that this is consistent with the *in situ* imine formation followed by boration and not direct boration of α,β-unsaturated ketone **1a** followed by imine formation of the resulting

β-boryl ketone **5a.** This early result demonstrates the asymmetric potential of the 4-step one-pot protocol for the synthesis of enantioenriched γ–amino alcohols. Moreover, the use of this new 4-step one-pot methodology opens the possibility to extend the substrate scope further, because the isolation of the α,β–unsaturated imines can be avoided.

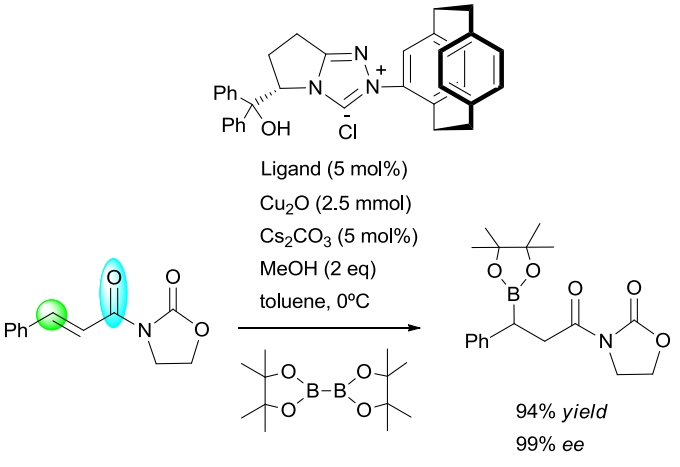


Scheme 3.19 *In situ* imine formation from ketone **1a**, followed by asymmetric β–boration.

3.6. Copper catalyzed base-free asymmetric β–boration used in the 4-step one-pot reaction sequence

The addition of base in the Cu-mediated β–borations of α,β–unsaturated compounds has always been required, [28] unless preformed (NHC)CuOR species (NHC= N-heterocyclic carbene ligands) and $Cu(OH)_2$/L are used to activate the B_2pin_2 [27-29] or sp^2-sp^3 hybridized mixed diboron reagents are applied, which can transmetallate directly with CuCl to provide the CuBpin reactive species. [30] We became interested in exploring the use of Cu_2O as precursor of the active catalytic system for the β-boration of α,β-unsaturated imines. Most importantly, this could potentially behave as a novel base-free system, and it can easly be made chiral with suitable chiral ligands. To the best of our knowledge,

there is only one example of asymmetric induction upon C-B bond formation mediated by Cu_2O and this is the β-boration of α,β-unsaturated *N*-acyloxazolidinones using a chiral bicyclic 1,2,4-triazolium salt as the precursor of the ligand (Scheme 3.20) and Cs_2CO_3 as the base. [31] Our objective was to investigate, and highlight the benefits of Cu_2O as a cheap catalyst precursor, avoiding the addition of an external base, and modify the Cu_2O with commercially available chiral ligands, such as (*R*)-BINAP, to promote an efficient enantioselective catalytic system for β–boration reactions and apply this new catalytic system to the 4 step one-pot protocol that we have described in the previously chapter.

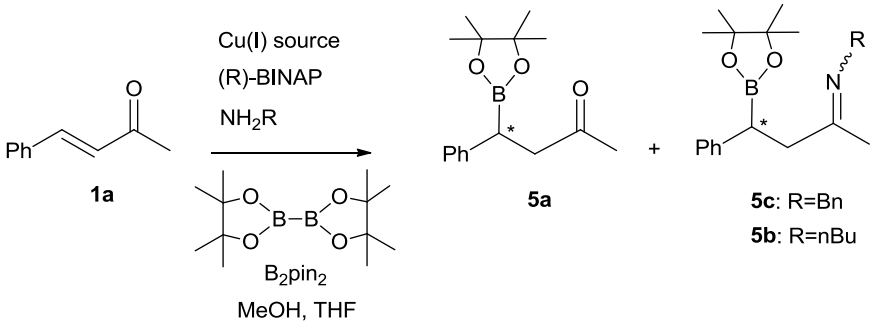


Scheme 3.20 Cu_2O mediated asymmetric β-boration of N-cinnamoyloxazolidin-2-one using a chiral triazoliuim salt as the precursor of the ligand.

Our study began with the β-boration of 4-phenyl-3-buten-2-one (**1a**) as a model substrate, and bis(pinacolato)diboron (B_2pin_2) as the diboron reagent. Two Cu(I) sources were selected, CuCl (3 mol%) and Cu_2O (1.5 mol%), in order to compare their relative activities as catalyst precursors, in the presence of (*R*)-BINAP. In an initial set of experiments, substrate **1a** was not converted into the β-borated ketone **5a** in the absence of $BnNH_2$ (Table 3.14, entries 1 and 6), however, with the addition of increasing amount of $BnNH_2$ (10 – 100 mol%) progressive formation of the β-borated imine **5c** occurred with different efficiency, depending on the copper source. When the CuCl-(*R*)-BINAP catalytic system was used, the

β-borated ketone **5a** was still the main product at low amine loadings (Table 3.14, entries 2-3). When the percentage of amine increased from 50 to 100% in the CuCl mediated reaction, only β-borated imine **5c** was observed, although some of the substrate **1a** still remained unreacted even in the presence of 100% of $BnNH_2$ (Table 3.14, entries 4-5). Remarkably however, when the Cu_2O-(*R*)-BINAP catalyst system was used for the β-boration of **1a**, the percentage of the β-borated imine **5c** formed was, in all cases, close to the percentage of amine present (Table 3.14, entries 7-10). This shows that Cu_2O favours trapping the "*in situ*" formed α,β-unsaturated imine by catalyzing its transformation into the corresponding β-borated imine **5c**. In addition, the beneficial influence of Cu_2O was also manifested in the asymmetric induction of the C-B bond formation step. While the CuCl-(*R*)-BINAP catalytic system provided the β-borated imine with *e.e.* values around 85-89%, the Cu_2O-(*R*)-BINAP system promoted the enantioselective formation on **5c** in up to 99 % of *e.e.* (Table 3.14). It is noteworthy also that the remaining β-borated ketone **5a** was obtained always with *e.e.* values between 16-22%, and that an excess of (*R*)-BINAP in the reaction media did not change the reaction outcome (Table 3.14, entry 11). Higher Cu_2O loadings, had no significant effect either (Table 3.14, entry 12). Interestingly to note that the corresponding Cu(II) precursor, CuO, was also tested. The CuO-(*R*)-BINAP catalytic system did convert the α,β-unsaturated ketone **1a** into the β-borated imine **5c**, however, with only 71% of conversion and 73% e.e. (Table 3.14, entry 13). It is worth noting that there are only two previous reports of Cu(II) catalysed β-boration of α,β-unsaturated carbonyl compounds [29], and to the best of our knowledge, this is the first example of Cu(II) catalyzed the β-boration of α,β-unsaturated imines. It is also important to note that the nature of the amine used in the reaction seems to be crucial for the enantioselection. For instance, when the β-boration of **1a** with Cu_2O-(*R*)-BINAP was carried out in the presence of 100 mol% of NH_2Bu, the β-borated imine **5a** was quantitatively formed, but only with 27% *e.e.* (Table 3.14, entry 14).

Table 3.14 Cu-(*R*)-BINAP mediates β-boration of activated olefins [a].



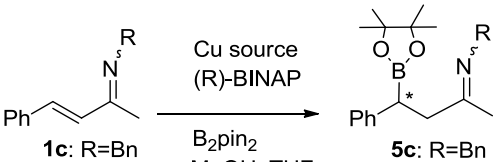
Entry	Cu(I)	RNH_2 (mol%)	Conv (%)[b]	5a (%)[b]	*e.e* (%)[c]	5c (%)[b] [*I.Y.*(%)]	*e.e* (%)[c]
1	CuCl	---	0	---	---	---	---
2	CuCl	$BnNH_2$ (10)	24	21	21 (*S*)	3	n.d.
3	CuCl	$BnNH_2$ (25)	35	32	22 (*S*)	3	n.d.
4	CuCl	$BnNH_2$ (50)	36	---	---	36	89 (*S*)
5	CuCl	$BnNH_2$ (100)	71	---	---	71	85 (*S*)
6	Cu_2O	---	0	---	---	---	---
7	Cu_2O	$BnNH_2$ (10)	43	37	16 (*S*)	6	99 (*S*)
8	Cu_2O	$BnNH_2$ (25)	53	32	22 (*S*)	21	99 (*S*)
9	Cu_2O	$BnNH_2$ (50)	57	11	nd	46	95 (*S*)
10	Cu_2O	$BnNH_2$ (100)	>99	0	nd	99	95 (*S*)
11[d]	Cu_2O	$BnNH_2$ (100)	>99	0	nd	99	93 (*S*)
12[e]	Cu_2O	$BnNH_2$ (100)	>99	0	nd	>99 [89]	95 (*S*)
13[f]	CuO	$BnNH_2$ (100)	71	0	nd	71	73 (*S*)
14	Cu_2O	n-$BuNH_2$ (100)	>99	---	---	99	27[g] (*S*)

[a] Reaction conditions: substrate (0.25 mmol), CuCl (3 mol%) or Cu_2O (1.5 mol%), (*R*)-BINAP (3 mol%), B_2pin_2 (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL) 25 ºC, 16 h. [b] Conversion and selectivity calculated from consumed substrate by ^1H NMR. [c] E.e. calculated by HPLC-UV as an average of two results. [d] Cu_2O (1.5 mol%), (*R*)-BINAP (6 mol%). [e] Cu_2O (3 mol%), (*R*)-BINAP (6 mol%). [f] CuO (3 mol%), (*R*)-BINAP (6 mol%). [g] E.e. calculated on the hydrolyzed ketone *via* HPLC-MS.

To confirm the benefits of Cu_2O-(*R*)-BINAP on the enantioselective formation of the β-borated imines, we became interested in isolating the α,β-unsaturated imines, such as (*E*)-1-phenyl-N-(4-phenylbut-3-en-2-ylidene)methanamine (**1c**), and performing the β-boration on that substrate to compare with the reactions carried out from the *in situ* reaction of α,β-unsaturated ketone **1a** + $BnNH_2$. In the

absence of base, Cu_2O-(*R*)-BINAP catalysed the formation of **5c** with high enantioselectivity, while CuCl-(*R*)-BINAP was inactive (Table 3.15, entries 1 and 2). The addition of 10 mol% NaO*t*Bu or Cs_2CO_3 to the CuCl-(*R*)-BINAP catalytic system favoured the formation of **5c**, but resulted in a racemic product (Table 3.15, entries 4 and 5). However, the addition of 10 mol% $BnNH_2$ as base did not favour the β-boration of the imine. The role of the base is expected to favour transmetallation between CuCl and B_2pin_2, [28] however, it seems that only inorganic bases assist this step. In contrast, when Cu_2O was used, no additional base was required to promote the transmetallation and in addition, the enantioselectivity was significantly higher.

Table 3.15. Cu-(*R*)-BINAP mediates β-boration of activated olefins [a].



1c: R=Bn
1b: R=Bu

5c: R=Bn
5b: R=Bu

Entry	Imine	Cu(I)	Base (mol%)	Conv (%)[b]	5 (%)[b] [*I.Y.*(%)]	*e.e* (%)[c]
1	**1c**	Cu_2O	---	>99	>99	87 (*S*)
2	"	CuCl	---	0	---	--
3	"	CuCl	$BnNH_2$ (10)	0	---	--
4	"	CuCl	$CsCO_3$ (10)	>99	>99	0
5	"	CuCl	NaOtBu (10)	>99	>99	0
6	"	$(CH_3CN)_4CuPF_6$	---	>99	>99	85 (*S*)
7	"	CuO	---	15	15	69 (*S*)
8	**1b**	Cu_2O	---	99	99	7[d] (*S*)
9	"	$(CH_3CN)_4CuPF_6$	---	99	99	8[d] (*S*)
10	"	CuCl	---	<5	---	--

[a] Reaction conditions: α,β-unsaturated imine (0.25 mmol), CuCl (3 mol%)/(*R*)-BINAP (6 mol%), $(CH_3CN)_4CuPF_6$ (3 mol%)/(*R*)-BINAP (6 mol%) or Cu_2O (1.5 mol%)/(*R*)-BINAP (3 mol%), B_2pin_2 (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL) 25 ºC, 16 h. [b] Conversion calculated from consumed substrate by ^{1}H NMR. [c] E.e. calculated by HPLC-UV as an average of two results. [d] *E.e.* calculated from the hydrolysed ketone via HPLC-MS.

The lack of a coordinating anion on the Cu(I) catalytic system appears to be the key factor in avoiding the need for additional base in the β-boration. This is clearly demonstrated by using $Cu(CH_3CN)_4PF_6$ modified with (*R*)-BINAP to catalyze the asymmetric β-boration of **1c** (Table 3.15, entry 6), which is similar to using Cu_2O, although Cu_2O is significantly cheaper. Interestingly, when Cu(II) was also explored for catalysing the reaction, we observed that the CuO-(*R*)-BINAP catalytic system was almost inactive towards the β-boration of **1c** (Table 3.15, entry 7). If we compare the latter result with the CuO-(*R*)-BINAP catalyzed β-boration of **1a** in the presence of 1 eq of $BnNH_2$ (Table 3.11, entry 13), we can conclude that the Cu(II) catalytic system studied needs a base to activate the diboron source. From these observations, it is clear that the use of Cu_2O is especially beneficial because it can be used in the absence of bases to promote the desired β-boration reaction. Considering the influence of the *N*-substituent, when Cu_2O-(*R*)-BINAP mediated the β-boration of (*E*)-N-(4-phenylbut-3-en-2-ylidene)butan-1-amine (**1b**), the β-borated imine **5b** was quantitatively formed, again, without the use of base, but the enantioselectivity was very low (Table 3.15, entry 8). Similar behaviour was observed when $Cu(CH_3CN)_4PF_6$ was the copper source. The CuCl provided inactive (Table 3.15, entries 9 and 10). The observation of low enantioselectivity in entries 8 and 9 (Table 3.15) also confirms the important role of the N-substituent in achieving high asymmetric induction.

The synergy between Cu_2O and (*R*)-BINAP (**L8**) was further demonstrated when we explored the influence of alternative bidentate chiral ligands such as (*R*)-Tol-BINAP (**L16**), (*R*)-Ph-MeOBiphep (**L14**), Josiphos (**L1**, **L5**) and Mandiphos (**L12**) type ligands. Remarkably, the cheapest ligand, (*R*)-BINAP, provided the best influence on the enantioselective Cu_2O-catalysed β-boration of 4-phenyl-3-buten-2-one **1a**, in the presence of 1 eq. of $BnNH_2$ and B_2pin_2 (Figure 3.13).

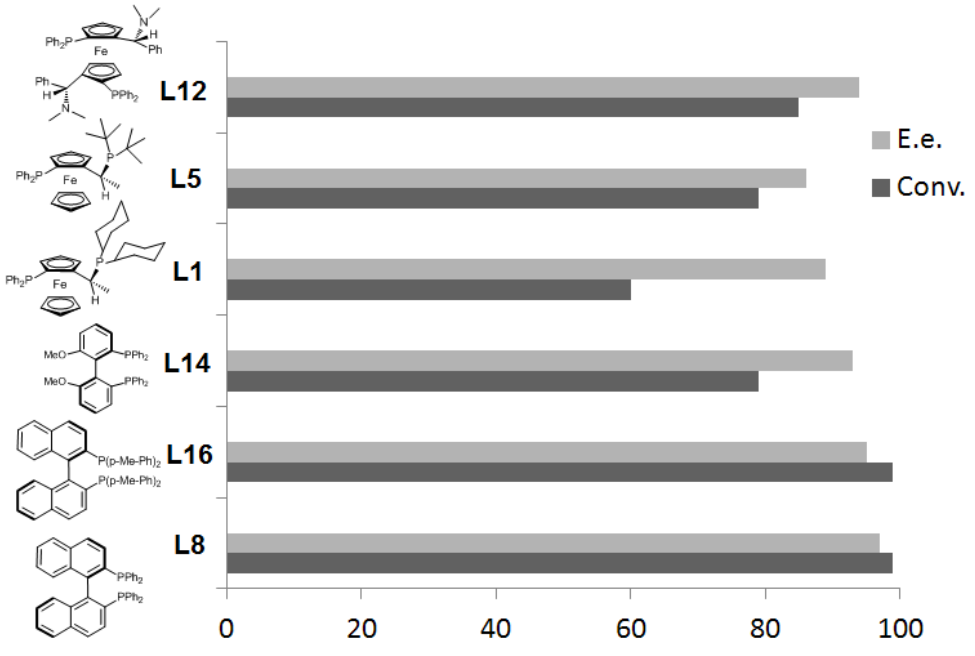
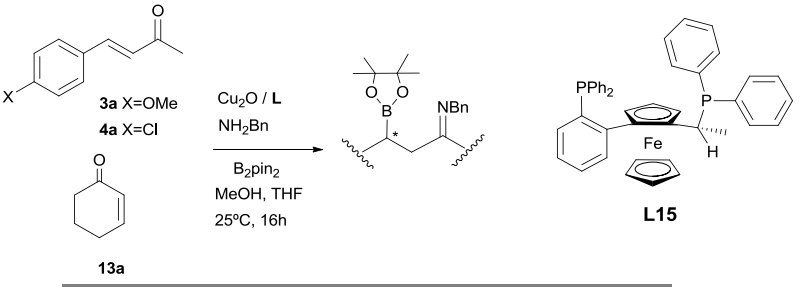
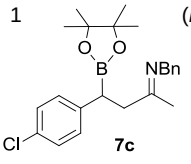
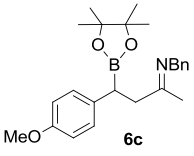
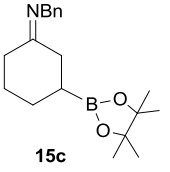
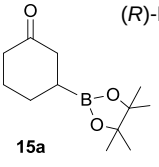


Figure 3.13. Cu_2O (1.5 mol%)/L (3 mol%), catalysed the β-boration of 4-phenyl-3-buten-2-one (**1**) (0.25 mmol), in the presence of $BnNH_2$ (1eq.) and B_2pin_2 (1.1 eq.), MeOH (2.5 equiv.), THF (1 mL) 25 ºC, 16h.

The substrate scope of the β-boration of α,β-unsaturated imines, formed *in situ* from the corresponding α,β-unsaturated ketones and $BnNH_2$, was surveyed using the Cu_2O-(*R*)-BINAP catalytic system, and compared also with the influence of alternative chiral ligands. For the transformation of 4-(*p*-MeO-phenyl)-3-buten-2-one (**2a**) into the β-borated imine **6c** (Table 3.16, entry 1), the Cu_2O-(*R*)-BINAP and Cu_2O-(*R*)-Tol-BINAP catalytic systems provided moderate conversions but high *e.e.s*. On the other hand, the Cu_2O system modified with the MeOBiphep (**L14**) and Mandiphos (**L12**) ligands favoured high conversions, but provided only moderate enantioselectivities. In the case of the more electron deficient olefin 4-(*p*-Cl-phenyl)-3-buten-2-one (**3a**) (Table 3.16, entry 2), all the catalytic systems explored provided a quantitative formation of the β-borated product **8c** with only moderate enantioselectivities.

Table 3.16. Substrate scope for the Cu_2O mediated asymmetric β-boration of *in situ*-formed α,β-unsaturated imines [a].



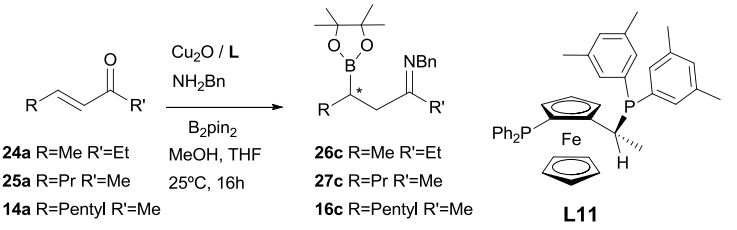
Entry	Product	Ligand	Conv (%)[b] [*I.Y.*(%)]	*E.e* (%)[c]
1	 7c	(*R*)-BINAP (**L8**)	67[45]	88 (*S*)
		L16	71	82 (*S*)
		L14	85[60]	49 (*R*)
		L12	99	35 (*R*)
2	 6c	(*R*)-BINAP (**L8**)	99 [87]	48 (*S*)
		L16	99	47 (*S*)
		L14	99 [85]	58 (*S*)
		L12	99	35 (*S*)
3	 15c	(*R*)-BINAP (**L8**)	99 [89]	39 (*S*)[d]
		L16	99	65 (S)[d]
		L14	97	30 (S)[d]
		L15	20	92 (*R*)[d]
4	 15a	(*R*)-BINAP (**L8**)	93 (2 h)	40 (*R*)[e]
		L16	93 (2 h)	63 (*S*)[e]
		L15	90 (24 h)	90 (*S*)[e]

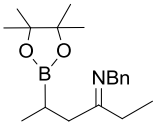
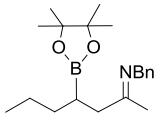
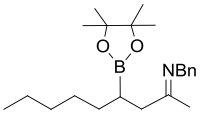
[a] Reaction conditions: α,β-unsaturated imine (0.25 mmol), Cu_2O (3 mol%), L (6 mol%), B_2pin_2 (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 ºC, 16 h. [b] Conversion calculated from consumed substrate by ^1H NMR spectroscopy. [c] E.e. calculated by HPLC-UV as an average of two results. [d] *e.e*. Calculated on the hydrolysed β-borated ketone *via* HPLC-MS. [e] Ref. 36, CuCl (3 mol%), NaO*t*Bu (3 mol%), L (3 mol%).

Having examined acyclic substrates, the β-boration of cyclic α,β-unsaturated imine substrates was also studied. We found that cyclohexenone (**13a**) could be efficiently converted into the desired product **15c** with Cu_2O-modified by (*R*)-BINAP (**L8**), (*R*)-Tol-BINAP (**L16**) and MeOBiphep (**L14**), however, the enantioselectivity was only moderate (Table 3.16, entry 3). In contrast, when the influence of a Walphos-type ligand **L15** was explored, we observed that although conversion to the product **15c** was low (20%), the *e.e.* was the highest for this substrate (92%) (Table 3.16, entry 3). It is interesting to note that although this is the first approach to the enantioselective formation of cyclic β-boryl imine derivatives, the *base-free* asymmetric induction provided by Cu_2O modified with ligands **L8**, **L16** and **L15** is in complete agreement with the previous work of Yun and coworkers, [32] who reported that CuCl mediated the enantioselective β-boration of cyclohexenone in presence of base (Table 3.16, entry 4). Since the corresponding α,β-unsaturated cyclic imine, 1-phenyl-*N*-(cyclohexenyl)methanamine, could not be isolated to be β-borated, this alternative route, that is, the *in situ* formation of the imine, followed by β-boration with the Cu_2O-based system, represents a simple method to obtain an enantiomerically enriched β-borated imine **15c**.

Another set of substrates we were keen to explore as suitable candidates for the *in situ* imine formation followed by β-boration, in the presence of Cu_2O/L, were the aliphatic, open-chain, α,β-unsaturated ketones, 4-hexen-3-one (**24a**), 3-hepten-2-one (**25a**) and *trans*-3-nonen-2-one (**14a**). The corresponding α,β-unsaturated imines could also not be isolated either, in order to perform a copper-catalyzed β-boration, and hence, the *in situ* protocol gave us an alternative synthetic route towards the aliphatic β-borated imines (see Table 3.17). In all cases, a secondary product (β-amino ketone) could be identified due to the competitive aza-Michael addition of the amine to the α,β-unsaturated ketones. [33] The chemoselectivity of the amine addition, that is, the spectroscopical yield of the desired β-borated imine, varied from moderate to high, depending on the substrate and the nature of the ligand.

Table 3.17. Substrate scope for the Cu_2O mediated asymmetric β-boration of in situ-*formed* α,β-unsaturated imines from aliphatic open chain α,β-unsaturated ketones [a].

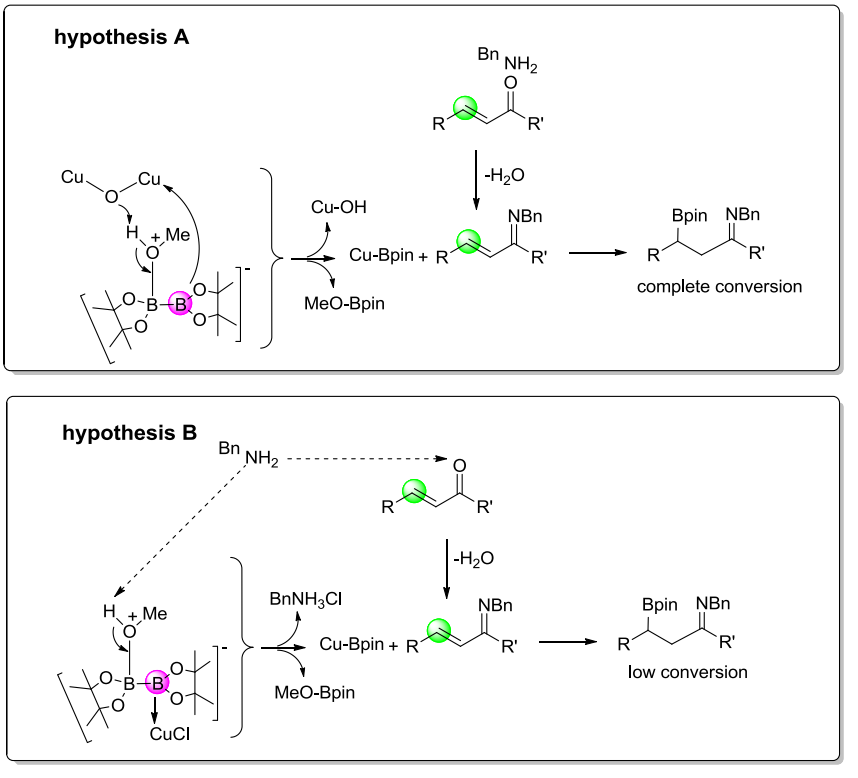


Entry	Product	Ligand	Conv (%)[b]	Sel(%)[c] [*I.Y.*(%)]	*E.e* (%)[d]
1	 **26c**	(*R*)-BINAP **(L8)**	99	55 [35]	66 (+)
		L16	99	63	61(+)
		L14	99	68 [32]	50 (+)
		L11	99	54	80 (+)
2	 **27c**	(*R*)-BINAP **(L8)**	99	70 [63]	62 (+)
		L16	99	93	60 (+)
		L14	99	90 [76]	64 (+)
		L11	99	52	73 (+)
3	 **16c**	(*R*)-BINAP **(L8)**	99	71 [56]	70 (+)
		L16	99	77	66 (+)
		L14	99	58 [43]	64 (+)
		L11	99	64	92 (+)

[a] Reaction conditions: α,β-unsaturated imine (0.25 mmol), Cu_2O (3 mol%), L (6 mol%), B_2pin_2 (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 ºC, 16 h. [b] Conversion calculated from consumed substrate by ^{1}H NMR spectroscopy. [c] Selectivity calculated by ^{1}H NMR spectroscopy, with the β-amino ketone as by-product. [d] *e.e.* Calculated via HPLC-MS.

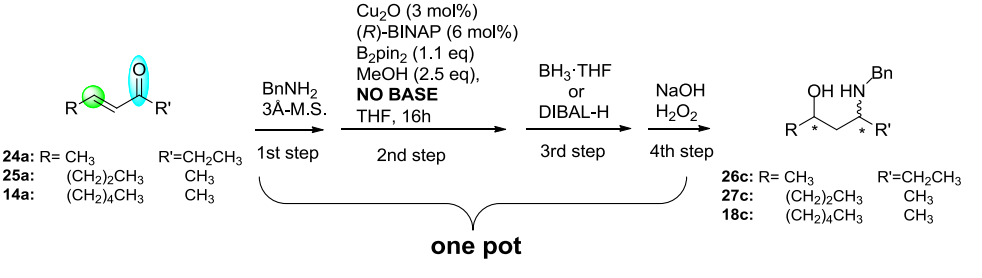
When the substrate was 3-hepten-2-one **25a**, the two-step transformation occurred efficiently to give the β-borated imine in high conversion (up to 93%, Table 3.17, entry 2). The bidentate chiral ligand which induced the highest enantioselectivity in the Cu_2O mediated imine formation / β-boration of ketones **24a** and **25a** was the Josiphos-type ligand **L11** (*e.e.s* up to 92%, Table 3.17).

Scheme 3.21 illustrates, in hypothesis **A**, a plausible interaction between Cu_2O, MeOH and B_2pin_2, to provide the corresponding CuBpin nucleophilic species and an additional Cu(OH) species ready to transmetallate further with B_2pin_2. In this hypothetical view, the NH_2Bn seems to be exclusively involved in the imine formation. However, when CuCl is used as the copper source, the $BnNH_2$ may have a partial role in inefficiently activating MeOH and forming the imine (Scheme 3.21, hypothesis **B**). This would explain why the reactions carried out without base addition and using CuCl do not proceed to completion effectively and low or zero activity that is observed in the β-boration of the isolated imine. Of course, the addition of base is able to restore the catalytic activity, but even this does not match the newly developed efficient Cu_2O system. In addition, the enantioselectivity could be increased by the absence of external base which favors background reactions.



Scheme 3.21 Hypothetical activation of B_2pin_2 with Cu_2O and CuCl.

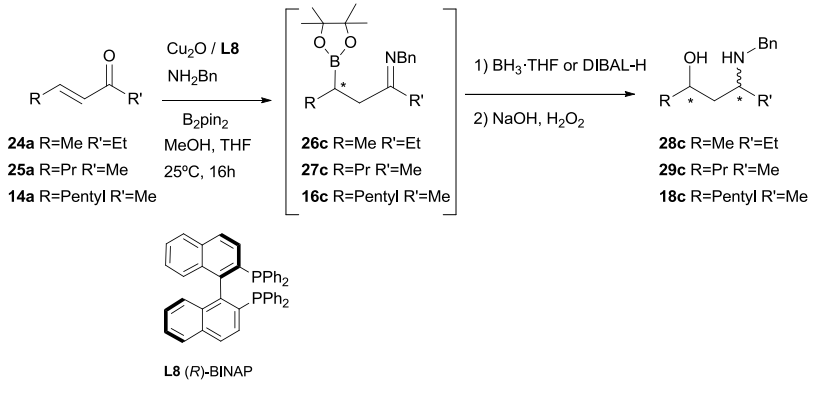
Finally, we completed the one-pot four step sequence towards the chiral γ–amino alcohols (Scheme 3.22).



Scheme 3.22 Imine formation/β-boration using Cu_2O and (*R*)-BINAP/reduction/oxidation is the new 4-step one-pot procedure to synthesize enantioenriched γ-amino alcohols.

We then concentrated our efforts to explore the transformation of **24a**, **25a** and **14a** into the corresponding γ–amino alcohol, by selecting the appropriate reducing agent to control the diastereoselectivity towards the *syn*-isomer (BH_3·THF and DIBAL-H). We observed that for the α,β–unsaturated ketone **24a**, a mixture of *syn*- and *anti*-isomer was obtained using BH_3·THF as reducing agent (Table 3.18, entry 1). However, the use of DIBAL-H improved the diastereoselectivity toward the *syn*-isomer (Table 3.18, entry 4). The α,β–unsaturated ketones **25a** and **14a**, have already a tendency to form the *syn*-isomer when BH_3·THF is used (Table 3.18, entries 2-3), but this tendency is increased with the use of the bulky reducing agent as DIBAL-H (Table 3.18, entries 4-5).

Table 3.18. Substrate scope for the Cu_2O mediated asymmetric β-boration of in situ-*formed* α,β-unsaturated imines from aliphatic open chain α,β-unsaturated ketones [a].



Entry	Product	Reducing agent	Conv% [b]	*e.e.*% [c]	Ds *Syn:anti* [d]	*I.Y.*%
1	**28c**	BH_3·THF	99	65	53:67	37
2	**29c**	BH_3·THF	99	58	63:37	42
3	**18c**	BH_3:THF	99	68	65:35	40
4	**28c**	DIBALH	99	63	69:31	-
5	**29c**	DIBAL-H	99	60	77:23	-
6	**18c**	DIBALH	99	67	81:19	52

[a] Reaction conditions: α,β-unsaturated ketone (0.25 mmol), NH_2Bn (0.25 mmol), Cu_2O (3 mol%), L (6 mol%), B_2pin_2 (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 ºC, 16 h. [b] Conversion calculated from consumed substrate by ^1H NMR spectroscopy. [c] e.e. Calculated via HPLC-MS. [d] Selectivity calculated by ^1H NMR spectroscopy, with the β-amino ketone as by-product.

In all the cases, the enantioselectivity induced in the β–boration of the *in situ* formed α,β–unsaturated imine could be conserved in the targeted γ–amino alcohol **28c, 29c** and **18c** (Table 3.18).

3.7 Conclusions

In this chapter, we have described the development and improvement of an one-pot reaction sequence to synthesize γ–amino alcohols with high control of the enantio- and diastereoselectivity. We can summarize the most important points as:

- ✓ An asymmetric simple, one-pot, three-step synthetic route consisted in β–boration/reduction/oxidation was established. The first and key step is the enantioselective β–boration of α,β–unsaturated imines. We identified several chiral phosphorus ligands which induce exceptional enantioselectivities in the copper catalyzed reaction. Using achiral reducing agents for the reduction of C=N double bond, we obtained total 1,3-diastereocontrol in the formation of both the *syn* and the *anti*-isomer.

- ✓ The comparative study of catalytic β–boration/reduction/oxidation of α,β–unsaturated ketones and imines has highlighted two important features: an intramolecular B-N interaction could favour the formation of the syn-diastereoisomer and that the asymmetric induction of the β–boration of α,β–unsaturated imines might be more successful than the corresponding α,β–unsaturated ketones. The imino group seems to provide a beneficial effect on the enantioselectivity of the reaction.

- ✓ An efficient one-pot 4-step protocol of the synthesis of γ–amino alcohols has been developed circumventing the isolation of the α,β–unsaturated imines. The potential of a 5-step one-pot route to 1,3-oxazines has also been demonstrated. This important approach was mainly developed in the team of Prof. Whiting (University of Durham).

- ✓ A new base free catalytic system, which utilizes Cu_2O as catalyst precursor, and efficiently catalyzes the β–boration of α,β–unsaturated compounds has been discovered. Excellent enantioselectivities are induced using cheap and

no high-sensitive ligands, such as (*R*)-BINAP. Applying these new conditions of β–boration to the one-pot 4-step procedure, we have obtained γ–amino alcohols and we have generalized this methodology.

3.8 References

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Chapter 4: Asymmetric metal free synthesis of β-amino alcohols

Table of contents

4.1 Introduction

Enantiomerically pure β–amino alcohols play an important role in pharmaceutical therapy and as chiral auxiliaries in organic synthesis. For instance, the β-amino alcohol derivatives Indinavir or Nelfinavir are currently being used as antiretroviral drugs for the treatment of human immunodeficiency virus (Figure 4.1). [1]

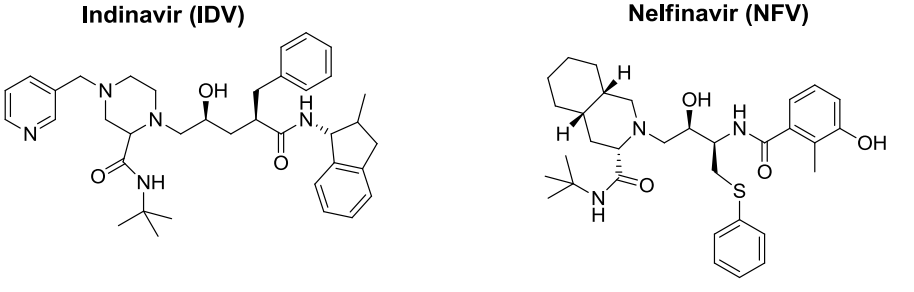


Figure 4.1 Structures of Indinavir and Nelfinavir drugs with HIV proteases inhibitors properties.

β-Amino alcohols are also applied as antibiotics. For example, ethambutol is a bacteriostatic antimycobacterial drug used for the treatment of tuberculosis (Figure 4.2). [2]

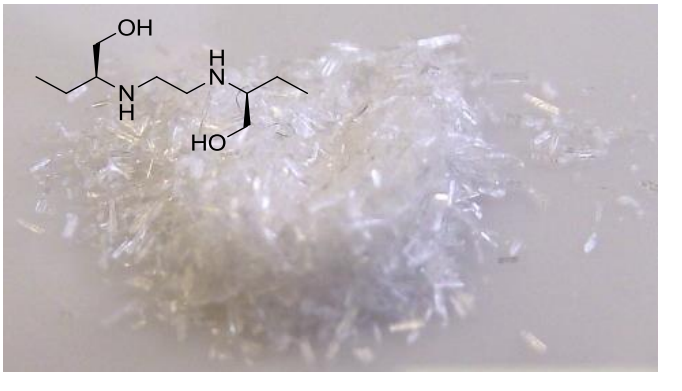


Figure 4.2 Structure and aspect of ethambutol.

In addition, β-amino alcohols are important structures in different natural products, such as lipids, [3] cyclic structures [4] or sugar moieties (Figure 4.3). [5] Yet β-

amino alcohol can be used as chiral ligands [6] or auxiliaries [7] in organic synthesis, as well, (Figure 4.4).

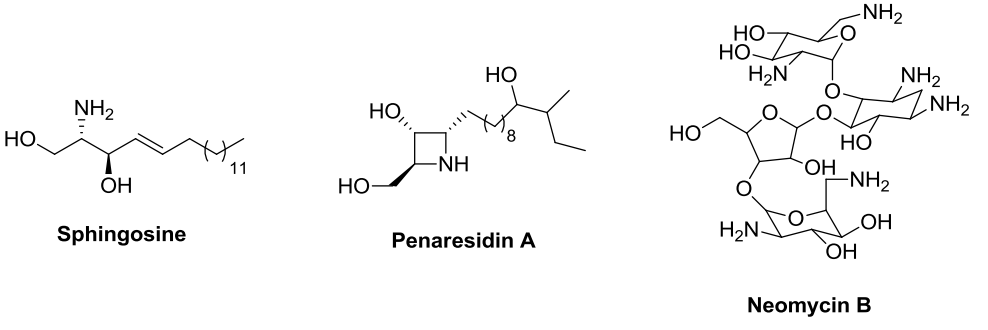


Figure 4.3 Examples of 1,2-amino alcohol moieties in natural products.

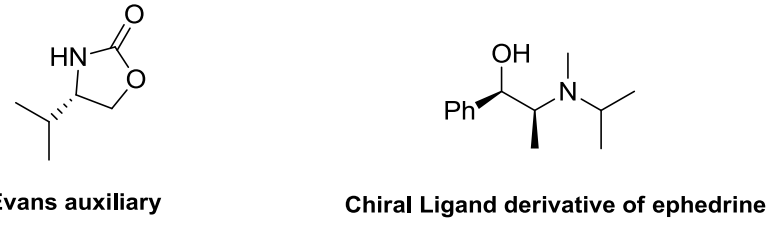
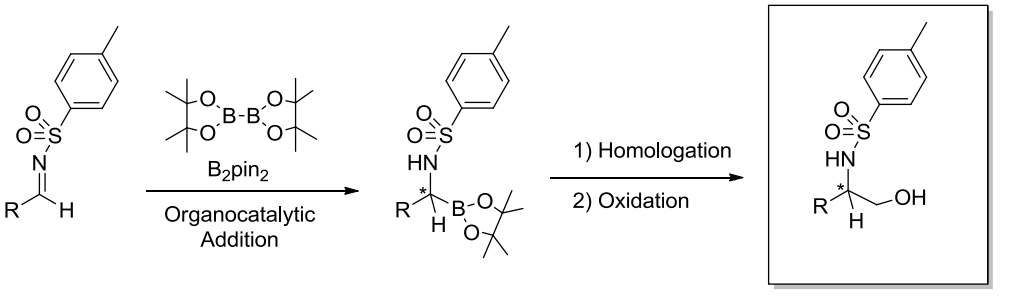


Figure 4.4 Amino alcohols used as chiral auxiliary and ligand in organic chemistry.

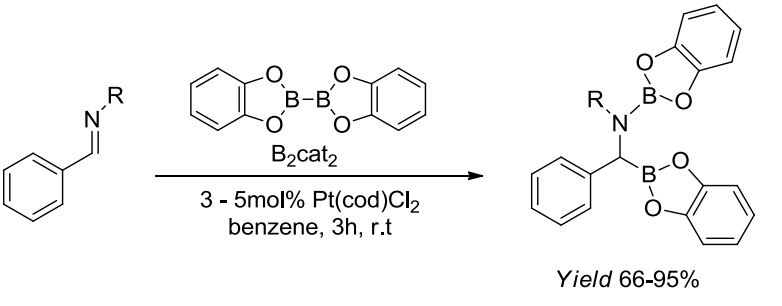
Taking into consideration the remarkable applications of β–amino alcohols, studies to develop direct asymmetric synthesis of β-amino alcohols, are more than justified.

Novel organocatalytic boron addition reactions recently developed by our research group, [8] served as the platform to design a new route towards β–amino alcohols. Conceptually, the new idea is based on the synthesis of α–amino boronates *via* organocatalytic pinacolboryl addition to tosyladimines followed by sequential homologation/oxidation reactions to obtain the desired β–amino alcohol (Scheme 4.1).



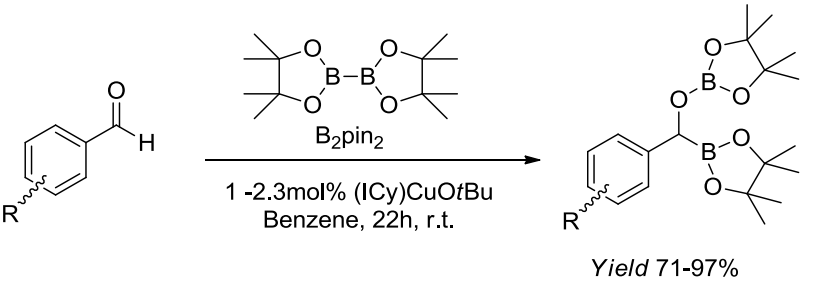
Scheme 4.1 New metal-free route towards the synthesis of β-amino alcohols.

To the best of our knowledge, when we started our study, the catalytic addition of diboron reagents to C=N bond, had only been attempted using transition metal complexes as catalysts. Specifically, the activation of bis(catecholato)diboron (B_2cat_2) by [Pt(cod)Cl_2] allowed the diboration of aldimines providing the first synthetic route towards *rac*-α-amino boronate esters (Scheme 4.2). [9]



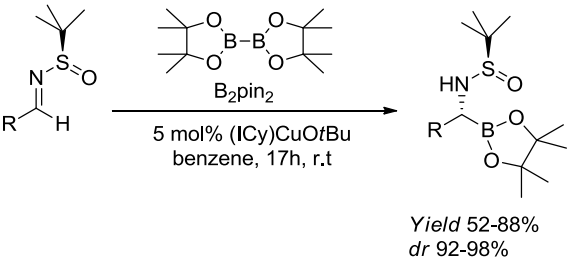
Scheme 4.2 Platinum-catalyzed diboration of aldimines.

Subsequently, the diboration catalyzed by copper complexes was explored by Sadighi and coworkers, [10] who used copper-alkoxide complexes modified with N-heterocyclic carbenes to activate bis(pinacolato)diboron (B_2pin_2) to form (NHC)CuBpin complexes, which catalyse the pinacolboryl addition to C=O in aldehydes (Scheme 4.3).



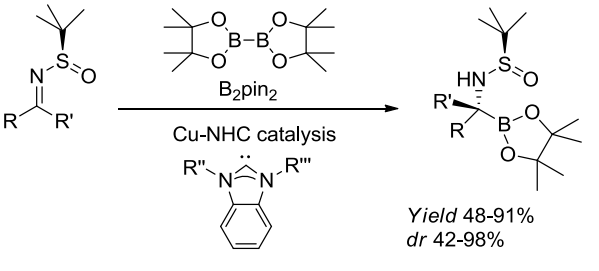
Scheme 4.3 Copper-catalyzed diboration of aldehydes.

Ellman and coworkers [11] followed the methodology of Sadighi and coworkers [10] successfully promoted diastereoselective Bpin addition to N-*tert*-butanesulfinyl aldimines using the catalytic system [(ICy)CuO*t*Bu] (ICy= 1,3-dicyclohexylimidazol-2-ylidene) (Scheme 4.4).



Scheme 4.4 Copper-catalyzed boron addition to N-*tert*-butanesulfinylaldimines.

Recently, Sun and coworkers [12] have improved the copper mediated pinacolboryl addition to N-*tert*-butanesulfinyl aldimines using benzimidazole-based NHC ligands that allow the efficient synthesis of α–amino boronic esters without the use of a glovebox to manipulate the catalytic system (Scheme 4.5).

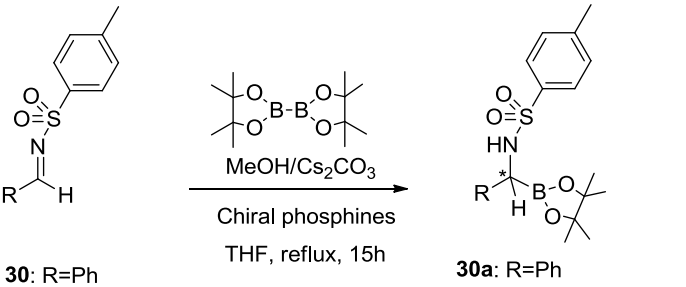


Scheme 4.5 Synthesis of α–amino boronic esters with stable Cu-NHC catalytic systems.

However, it was also reported that in the absence of transition metal complexes, the N-*tert*-butanesulfinyl aldimines could not be transformed into the desired N-sulfinyl α-amino pinacolboronate esters. [11] Consequently, the development of a metal-free boron addition to C=N double bonds was a challenging project.

4.2 Organocatalytic boron addition to tosylaldimines

In our ongoing research, we focus on the enantioselective introduction of boryl moieties into unsaturated substrates. Recently, we have found that methoxide anion activates B_2pin_2 to promote a nucleophilic boron addition to both activated [8a,c] and non-activated olefins. [8b] We have also observed that the use of chiral phosphines is an efficient way to induce asymmetry in the organocatalytic β-boration of α,β-unsaturated carbonyl compounds. [8a] Based on the experience we have accumulated in the asymmetric organocatalytic boron addition reactions, we intended to develop a synthetic route towards α-amino boronate esters *via* metal-free nucleophilic boryl addition to tosylaldimines. We planned to use the *in situ* formed MeO^- →bis(pinacolato)diboron adduct as a boron nucleophile, and we expected to be able to induce asymmetry with catalytic amounts of chiral phosphines (Scheme 4.6).



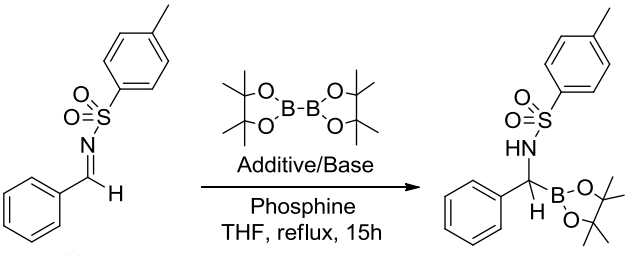
30: R=Ph
31: R=p-OMe-C_6H_4
32: R=p-F-C_6H_4
33: R=C_6H_{13}
34: R=Cy
35: R=2-Py

30a: R=Ph
31a: R=p-OMe-C_6H_4
32a: R=p-F-C_6H_4
33a: R=C_6H_{13}
34a: R=Cy
35a: R=2-Py

Scheme 4.6 Asymmetric organocatalytic boron addition to synthesize α–amino boronate esters.

We used N-benzylidene-benzenesulfonamide (**30**) as model substrate, and we activated B_2pin_2 with an excess of MeOH and catalytic amount of base to guarantee the *in situ* formation of the $MeO^-\rightarrow B_2pin_2$ adduct. [8c,d] Within 15h, at reflux temperature, 70% of the substrate was transformed into the corresponding α-amino boronate ester (Table 4.1, entry 1).

Table 4.1 Organocatalytic pinacolboryl addition from B_2pin_2 to N-benzylidene-benzenesulfonamide [a].



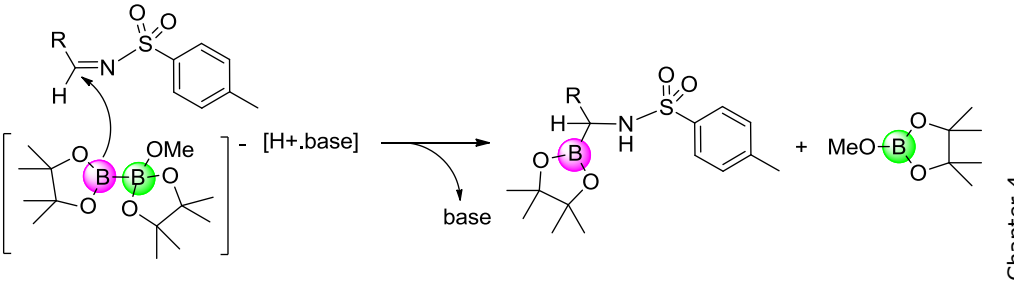
30 **30a**

Entry	Base	Phosphine	Additive	Conv (%) [b]
1	Cs_2CO_3	---	MeOH	70
2	Cs_2CO_3	PPh_3	MeOH	91 (78)[c]
3	Cs_2CO_3	PPh_3	---	---
4	---	PPh_3	MeOH	---
5	K_2CO_3	PPh_3	MeOH	83
6	KOH	PPh_3	MeOH	58
7	KOMe	PPh_3	MeOH	88
8	LiOMe	PPh_3	MeOH	89
9	NaOMe	PPh_3	MeOH	88
10	NaO*t*Bu	PPh_3	MeOH	85
11	Cs_2CO_3	PPh_3	PhOH	89
12	Cs_2CO_3	PPh_3	*i*PrOH	83
13	Cs_2CO_3	PPh_3	BuOH	78

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), phosphine (4 mol%), base (15 mol%), MeOH (2.5 eq.), THF (1 mL), 70ºC, 15 h. [b] Conversion calculated using ^1H NMR spectroscopy. [c] Isolated yield from 1 mmol of substrate.

The addition of a phosphine (PPh_3) resulted in higher conversion (up to 91%), but only when base and methanol were also present in the medium, otherwise no activity was observed (Table 4.1, entries 2-4). The obvious beneficial effect of PPh_3 on the activity prompted us to complement our catalytic system with

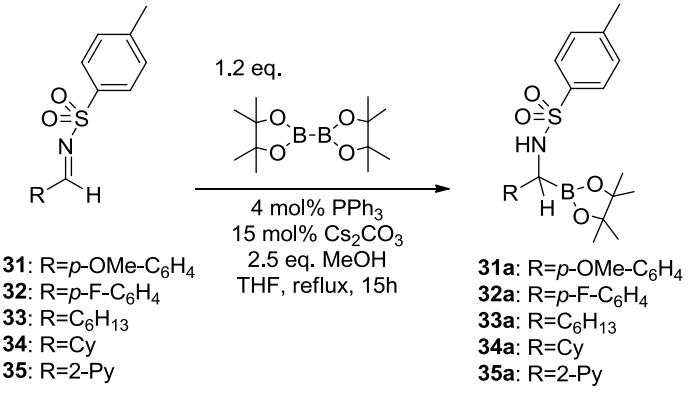
the phosphine. To further optimisation of the methodology, a number of bases and protic additives were screened. We found that MOMe (M = Li, Na, K) could be reasonable alternatives to Cs_2CO_3 (Table 4.1, entries 5-10). We expected that the nature of the alcohol additive will have a more direct influence on the reaction outcome, as it is assumed that the alkoxide ion, which interacts with the B_2pin_2, is generated from the alcohol. We examined alcohol additives of different pKa values and steric properties but none of them could outperform the originally chosen MeOH (Table 4.1, entries 11-13). It is important to note at this point that when the α,β–unsaturated imine (*E*)-N-benzylidene-1-phenylmethanamine (**1c**) was used as substrate in the organocatalytic boron addition reaction, the nucleophilic attack of the pinacolboryl, from the $MeO^-\rightarrow B_2pin_2$ adduct, did not take place. The efficiency of the pinacolboryl addition to the tosylaldimines, might be due to the beneficial electronic influence of the tosyl substituent on the N atom (Scheme 4.7).



Scheme 4.7 Organocatalytic nucleophilic pinacolboryl attack from *in situ* generated $MeO^-\rightarrow B_2pin_2$ to C=N double bond.

Using the optimized conditions, we performed organocatalytic pinacolboryl addition to a series of tosylaldimines (**31-35**), achieving high to quantitative conversions into the corresponding α-amino boronate esters, often even with only 6 hours of reaction time (Table 4.2). The presence of electron withdrawing substituents on the aryl groups or the lack of conjugation in the case of aliphatic tosylaldimines, clearly facilitated the nucleophilic addition (Table 4.2, entries 2,3).

Table 4.2. Organocatalytic pinacolboryl addition from B_2pin_2 to tosylaldimines [a].



Entry	Substrate	Product	Time (h)	Conv (%) [b]	Yield (%) [c]
1	**31**	**31a**	6/15	80/84	62
2	**32**	**32a**	6/15	95/99	79
3	**33**	**33a**	6/15	99/99	82
4	**34**	**34a**	6/15	31/40	20
5	**35**	**35a**	6/15	61/90	68

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), PPh_3 (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL), 70ºC. [b] Conversion calculated using ^1H NMR spectroscopy. [c] Isolated yield from 1 mmol of substrate.

4.3 Asymmetric borylation of tosylaldimines

In search of asymmetric induction in the C-B bond formation, we conducted a preliminary study with 2 mol% of the chiral diphosphine Walphos (*R*)-W001 (CF_3) (**L1**), which allowed the transformation of the substrate **30** into the α-amino boronate ester with 94% of *e.e.* at room temperature (Figure 4.5, bar 5). The enantioselectivity slightly decreased at higher temperatures but the activity significantly increased (Figure 4.5, bars 3-5). We should also highlight that, under identical reaction conditions, the metal free approach was more enantioselective than the analogous Cu(I)/**L1** catalyzed reaction (2 mol% loading), which provided only 66% of *e.e.* at room temperature (Figure 4.5, bars 1-2). Interestingly, it has been reported that when Cu(I)/**L1** mediated the asymmetric boration of α,β-unsaturated β-methyl sulphones, the conversion and *e.e* values were only moderate (76% and 40%, respectively) despite the fact that 10 mol% of copper salt/chiral ligand and 15 mol% of base, were used. [13]

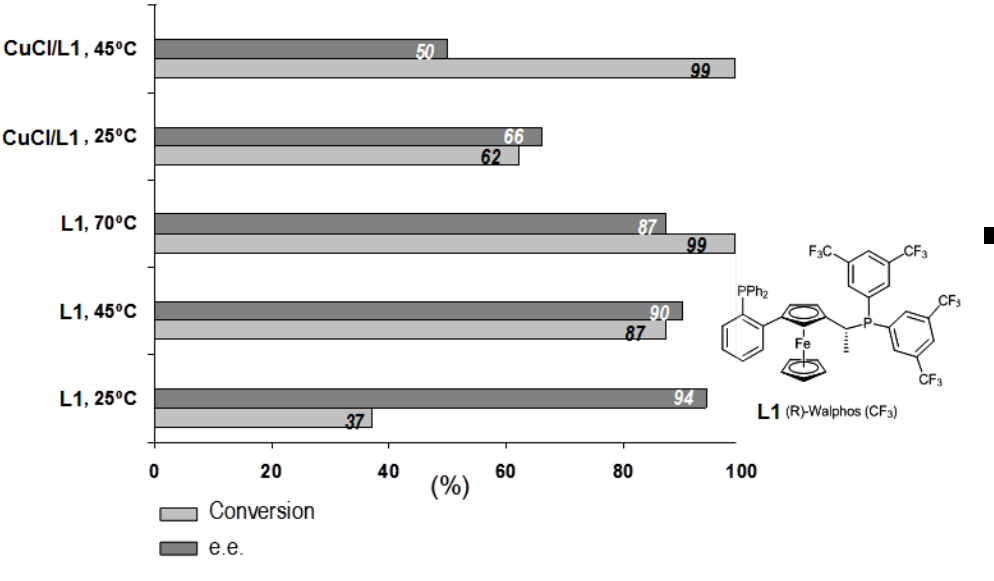
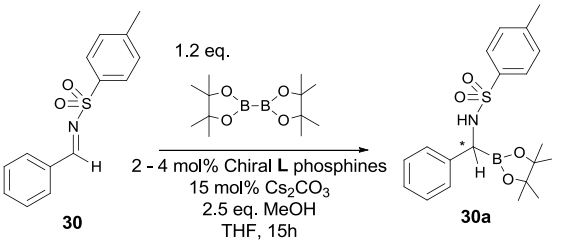
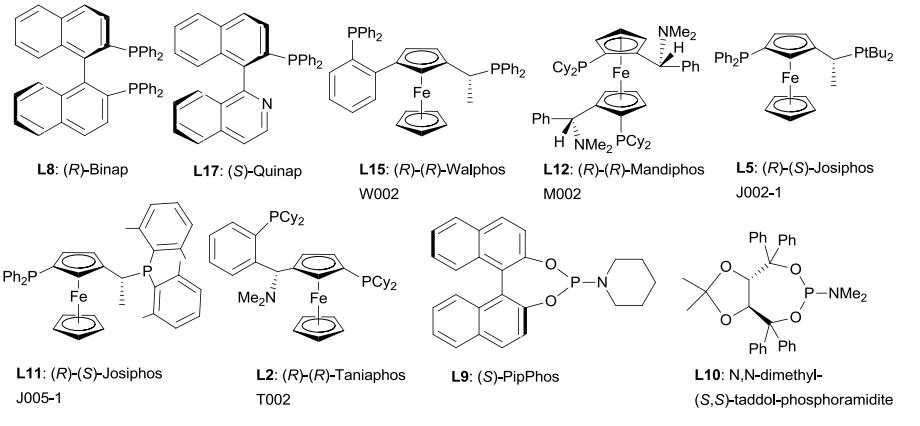


Figure 4.5 Enantioselective organocatalytic pinacolboryl addition from B_2pin_2, to **30** with **L1** versus the Cu(I)/**L1** catalyzed reactions. Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), **L1**(2 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL), CuCl (2 mol% when applied).

To identify alternative chiral catalysts we screened a small library of phosphines and phosphoramidites. Therefore, the most efficient enantioselective nucleophilic attack of Bpin, from the *in situ* generated $MeO^- \rightarrow B_2pin_2$ adduct, to N-benzylidene-benzenesulfonamide (**30**) could be performed in the presence of 2 mol% of (*R*)-Binap (**L8**), or (*S*)-Quinap (**L17**) (Table 4.3, entries 1 and 2). Chiral ferrocenyl type diphosphines (**L2, L5, L12, L11, L15**) and phosphoramidite ligands (**L9** and **L10**) resulted less efficient chiral additives (Table 4.3, entries 3- 9). In order to find a compromise between the activity and the enantioselectivity of the organocatalytic system, we performed the reactions at room temperature with 4 mol% loading of chiral phosphines and 24h of reaction time. Moderate conversions were observed but a significant increase in the enantioselectivities up to 99% were achieved when Walphos (*R*)-W001 (CF_3) (**L1**) and (*S*)-Quinap (**L17**) were applied (Table 4.3, entries 10-13).

Table 4.3. Enantioselective organocatalytic pinacolboryl addition to N-benzylidene-benzenesulfonamide (**30**) [a].



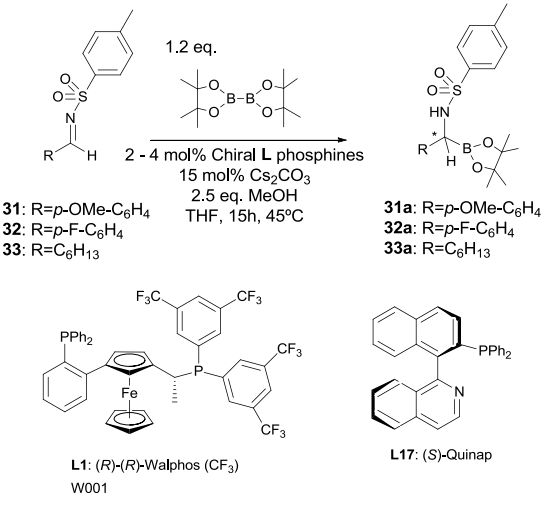


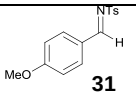
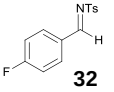
Entry	T(ºC)	Aux.(mol%)	t (h)	Conv (%) [b]	*e.e.*(%) [c]
1	45	**L8** (2)	15	88	67 (+)
2	"	**L17** (2)	"	99	41 (+)
3	"	**L15** (2)	"	63	72 (+)
4	"	**L12** (2)	"	19	85 (+)
5	"	**L5** (2)	"	35	60 (+)
6	"	**L11** (2)	"	23	70 (+)
7	"	**L2** (2)	"	33	86 (+)
8	"	**L9** (2)	"	40	90 (+)
9	"	**L10** (2)	"	55	79 (+)
10	25	**L1** (4)	24	56	99 (+)
11	"	**L8 (4)**	"	80	65 (+)
12	"	**L17** (4)	"	45	99 (+)
13	"	**L12** (4)	"	47	80 (+)

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), Chiral phosphine (2 or 4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL). [b] Conversion calculated using ^1H NMR spectroscopy. [c] *e.e.* determined by HPLC-TOF

The scope of the enantioselective organocatalytic reaction was established with the related tosylaldimines **31-33**, using **L1** and **L17** as chiral phosphines (Table 4.4). At 45ºC, the aliphatic tosylaldimine was transformed into the corresponding α-amino boronate ester with a considerably lower enantioselectivity than the aromatic substrates.

Table 4.4 Enantioselective organocatalytic pinacolboryl addition to tosylaldimines [a].



Entry	Substrate	Chiral Aux.	Conv (%) [b]	*e.e.* (%) [c]
1	 **31**	**L1**	83	75
2	"	**L17**	74	55
3	 **32**	**L1**	95	71
4	"	**L17**	90	52
5	 **33**	**L1**	97	24
6	"	**L17**	99	14

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), Chiral phosphine (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 mmol), THF (1 mL), 45ºC, 15h. [b] Conversion calculated using ^1H NMR spectroscopy. [c] *E.e*. determined by HPLC –TOF.

4.4 Transformation of an organoboron intermediate into β-amino alcohol

It is well known that chiral α-amino boronate esters have a tremendous scope of applications in pharmacology [14] since the discovery of the anticancer drug bortezomib (Velcade) by Julian Adams and coworkers (Figure 4.6). [15]

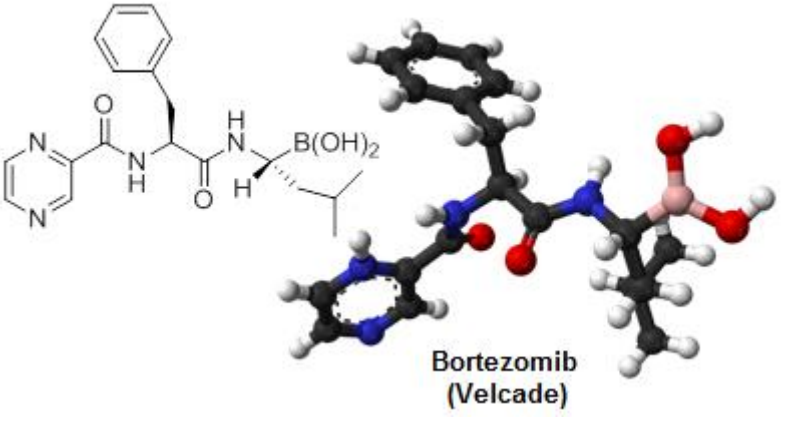
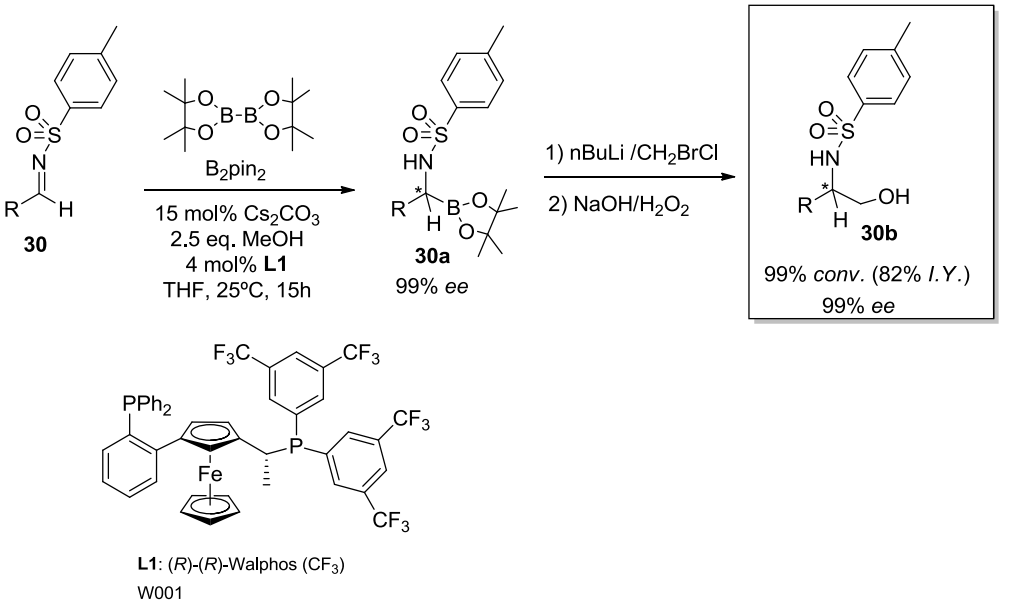


Figure 4.6 The 2D and 3D structure of drug Velcade using for the treatment of multiple myeloma.

In order to contribute to the development of chiral β–amino alcohols, we developed a simple one-pot transformation from the tosylaldimines using the enantioselective organocatalytic boryl addition to the C=N double bond followed by homologation/oxidation.

We tested the efficiency of this reaction sequence with the treatment of the α-amino boronate ester intermediate (achieved in 99% *e.e.* Table 4.3, entry 10) with CH_2BrCl/*n*-BuLi and $NaOH/H_2O_2$. [16] The procedure resulted in the formation of the corresponding 1,2-amino alcohol in 99% *e.e.* indicating that the optical purity was completely preserved during the reaction sequence (Scheme 4.8).



Scheme 4.8 The enantioselective organocatalytic boryl addition to C=N followed by homologation/oxidation to synthesize β–amino alcohols.

This new synthetic procedure opens a strategic avenue towards the asymmetric synthesis of the very versatile 1,2-amino alcohols [17] and complements the current synthetic strategies based on transition metal- and organocatalytic reactions. [18]

4.5 Conclusions

In this chapter, we have described the first organocatalytic nucleophilic addition of bis(pinacolato)diboron to tosylaldimines which results in the formation of α–amino boronate esters. We have been able to modify the organocatalytic system with chiral phosphines to induce asymmetry in the formation of the procut (*e.e*. values up to 99%).

In addition, taking into consideration the interesting applications of β–amino alcohols, we have applied a sequential homologation/oxidation procedure to derivatize the chiral α–amino boronate esters. The procedure provides the corresponding chiral β–amino alcohols preserving the enantiomeric excess of the organoborane intermediate. This simple one-pot reaction sequence represent an efficient route towards chiral β–amino alcohols.

4.6 References

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Chapter 5: Catalytic amination through boron chemistry

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5.1 Introduction

The activation of diboron reagents by other species different than transition metal complexes is a current challenge. In fact, the first metal free catalytic activation of tetraalkydiboron reagents was reported by Santos and coworkers in 2009 by an intramolecular activation with base (Figure 5.1). [1]

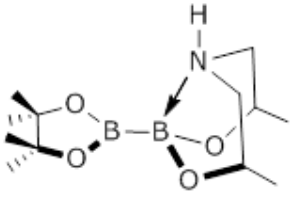
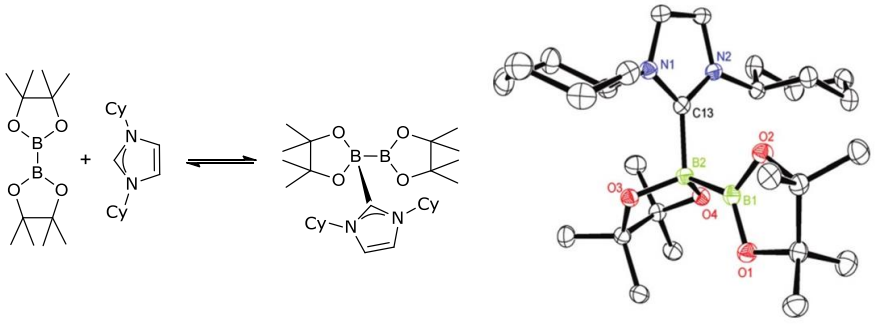


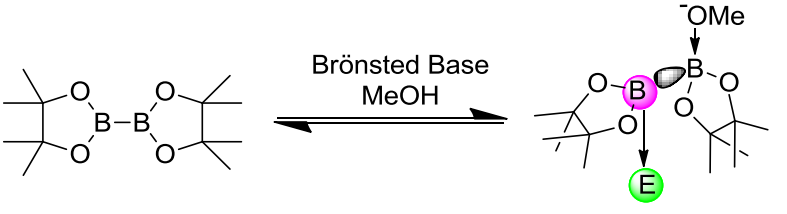
Figure 5.1 Activated diboron adduct by Lewis acid-base intramolecular interaction.

Further work by Hoveyda and coworkers demonstrated that carbenes could also interact with diborons. [2] In addition, the spectroscopic and theoretical studies by Marder and coworkers [3] eventually verified the existence of the neutral Lewis acid-base adduct of B_2pin_2 and the NHC (1,3-is(cyclohexyl)imidazol-2-ylidene) both in solution and in the solid state (Scheme 5.1).



Scheme 5.1 Crystal structure of the B_2pin_2·NHC adduct isolated by Marder and coworkers.

Simultaneously with Hoveyda's first report, some members of our group developed a new organocatalytic methodology based on the sole use of base and methanol as catalytic system. [4] Upon interaction of a Brönsted base with methanol, methoxide is generated, which interacts with the diboron reagent and forms the Lewis acid-base adduct [$MeO^- \rightarrow B(OR)_2$-$B(OR)_2$], facilitating the release of a boryl moiety with enhanced nucleophile character (Scheme 5.2).



Scheme 5.2 Activation of diboron reagent wit base/MeOH.

The element boron can be associated with other element to form heteroelement-element linkages as B-Si, B-Sn or B-Ge (Figure 5.2). [5] They are activated using transition metals [6], however, the B-Si interelement bond can also be transferred by the sole addition of catalytic amounts of donor reagents.

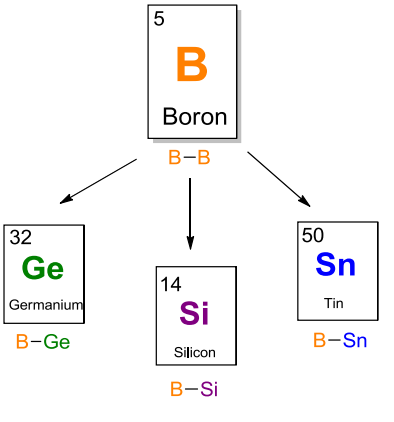
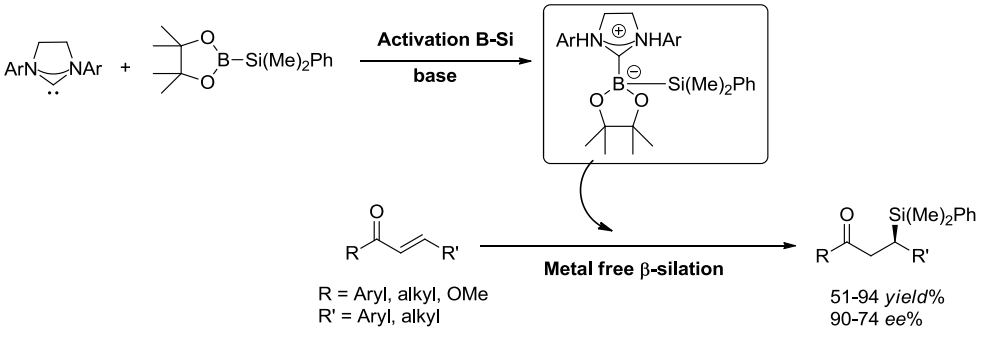


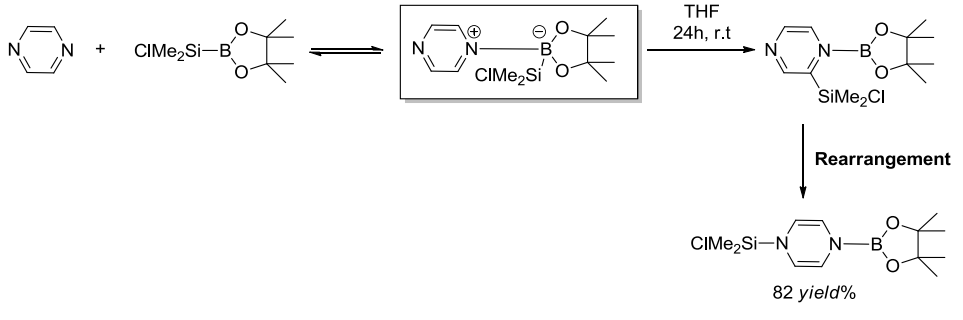
Figure 5.2 Interelement compounds from boron, germanium, silicon and tin.

Hoveyda and coworkers reported the first NHC-catayzed silyl conjugate addition to α,β-unsaturated carbonyl compounds where the B-Si bond was activated by N-heterocyclic carbenes (Scheme 5.3). [7]



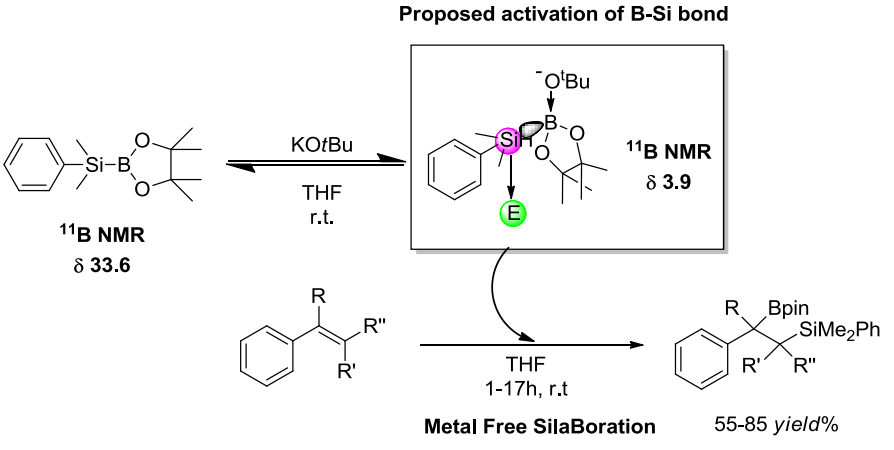
Scheme 5.3 NHC-Catalyzed Silyl Conjugate Addition to unsaturated carbonyls.

Pyrazines and substituted pyrazines interact with B-Si or B-B bonds, under transition-metal free conditions, to promote the 1,4-silaboration or 1,4-diboration (Scheme 5.4). [8]



Scheme 5.4 1,4-SilaBoration of substituted pyrazines

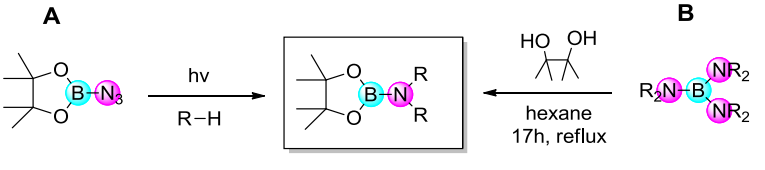
Recently, Ito and coworkers have reported the activation of B-Si using potassium *tert*-butoxide to promote the silaboration of aromatic alkenes (Scheme 5.5). [9] The NMR experiments supported the complexation of the silylboron and the alkoxide.



Scheme 5.5 Base-mediated silaboration of aromatic alkenes.

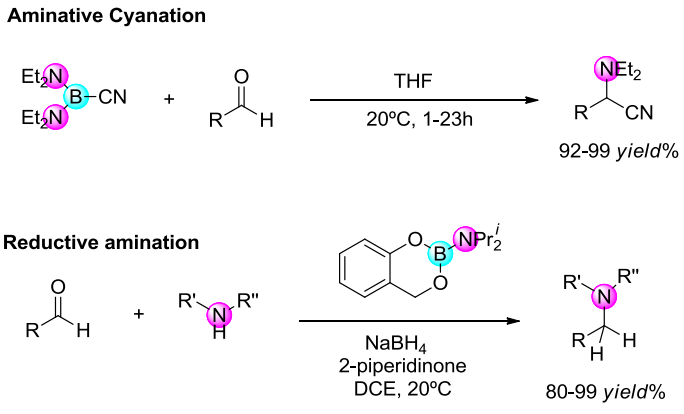
In this context, we became interested to study the possible Lewis acid-base interaction between aminoboranes, of formula $(RO)_2B\text{-}NR'_2$, and alkoxides to increase the nucleophilic character of the amine group towards organic electrophiles.

Aminoboranes have been previously synthesized from $B(NR_2)_3$ (Scheme 5.6b) [10] or borylnitrenes (Scheme 5.6a) [11] and applied in organic synthesis to generate organoboron compounds. [12]



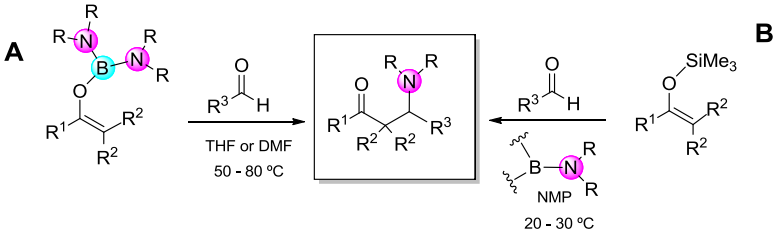
Scheme 5.6 Two synthetic routes to obtain aminoboranes.

Suginome and co-workers efficiently demonstrated the use of aminoboranes derivatives in amination reaction [13] such as Strecker-type aminative cyanation, [14] reductive amination (Scheme 5.7), [15] and Mannich type reaction. [16]



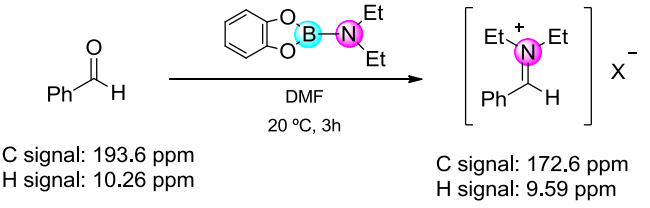
Scheme 5.7 The use of aminoboranes in amination reactions.

Following the latter methodology, a series of β-amino ketones and esters have been synthesized by reacting bis(dialkylamino)boron enolates with aldehydes [16a] (Scheme 5.8a) or silyl ketene acetals with aldehydes and aminoboranes [16b] (Scheme 5.8b).



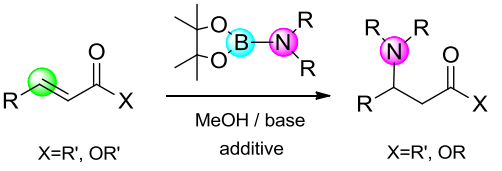
Scheme 5.8 Synthesis of β–amino ketones and esters using aminoboranes.

They postulated that the function of the amino-substituted boron compound was related to the generation of iminium ion, from the carbonyl compounds. Their proposed mechanism was supported by NMR experiments wherein new chemical signal shifts were observed and assigned to the iminium proton and carbon (Scheme 5.9). [16b]



Scheme 5.9 Proposed mechanism towards the formation of iminium salt with the aminoborane.

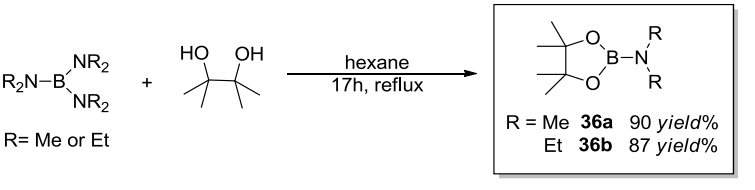
With this information in mind, we became interested in developing a new method for the preparation of β-amino carbonyl compounds by the simple Lewis acid-base interaction of aminoboranes with alkoxides, forming *in situ* the adduct [RO^- →$B(OR)_2$-$N(R')_2$], and enhancing the nucleophilic character of the amino group to selectively react with α,β-unsaturated carbonyl compounds (Scheme 5.10).



Scheme 5.10 New methodology to synthesize β–amino ketones via formation of the [RO^-→$B(OR)_2$-$N(R')_2$] adduct.

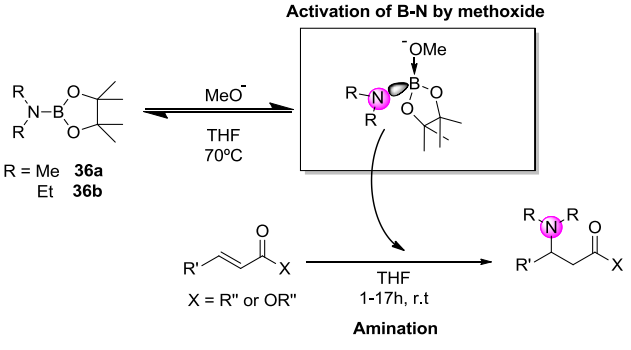
5.2 The pull-push effect of B in aminoboranes towards selective amination

Firstly, we synthesized two different aminoboranes *via* the reaction of pinacol and amines to form $B(NMe_2)_3$ and $B(NEt_2)_3$. [10b,c] The major affinity of the boron to the two oxygen of pinacol, allows the formation of the final desired aminoboranes with high yield (Scheme 5.11).



Scheme 5.11 Methodology to synthesize aminoboranes **36a** and **36b**.

After purification and characterization, the aminoboranes (**36a** or **36b**) were able to be activated by alkoxides. We also studied their reactivity with a diverse type of electrophiles, such as α,β–unsaturated ketones and esters (Scheme 5.12).

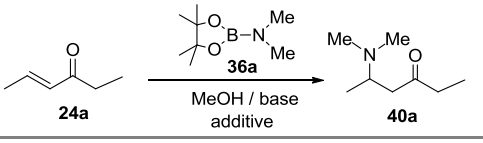


Scheme 5.12 Proposed activation and reactivity of aminoboranes **36a** and **36b**

The optimal conditions were sought for the amination of 4-hexen-3-one **24b** with Bpin-NMe_2 **36a** (Table 1). When the reaction was carried out in MeOH as solvent, in the absence of any other additives, at 70ºC, no amination product was observed (Table 5.1, entry 1). The addition of 5 mol % of NaO*t*Bu favoured the formation of 5-dimethylamino-hexan-3-one **40a** as the only product, with 28% of conversion (Table 5.1, entry 2). This is in agreement with the fact that the base reacts with MeOH to generate the alkoxide [4b] which might interact with the aminoborane to form a nucleophilic Lewis acid-base adduct. The addition of a phosphine as additive (10 mol% of PCy_3) had a beneficial effect on the catalytic activity, increasing the conversion of the substrate into the desired product up to 95% (Table 5.1, entries 3-7). The role of the phosphine has been associated to interact with the α,β-unsaturated carbonyl substrate resulting in the formation of a strongly basic zwitterionic phosphonium enolate species. [3c] However, the sole addition of phosphine, without base, does not guarantee the β-amination reaction (Table 5.1, entry 8). Temperatures about 70ºC seems to be required to guarantee a high transformation of the substrate **24a** into the β-amino ketone **40a** (Table 5.1, entries 4 and 9). The beneficial influence of MeOH being used as solvent versus THF + 2 eq. of MeOH as additive, has also been demonstrated (Table 5.1, entries 4 and

10). The nature of the base was also studied and under optimized conditions Cs_2CO_3 resulted also efficient to promote the amination of **24a** (Table 5.1, entry 11). Overall, the reaction conditions shown in Table 5.1 entry 6 were found to be optimal for the extension of the methodology to other α,β-unsaturated carbonyl compounds.

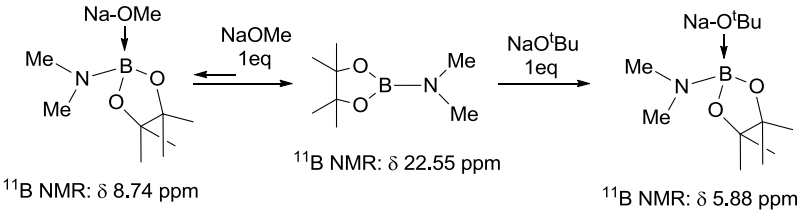
Table 5.1. Optimization of reaction conditions for the β-amination of 4-hexen-3-one with Bpin-NMe_2 (**36a**) [a].



Entry	Base (mol%)	Additive (mol%)	Solvent / T (ºC)	Conv(%)[b] [*I.Y.*(%)]
1	---	---	MeOH / 70	---
2	NaO*t*Bu(5)	---	MeOH / 70	28
3	NaO*t*Bu(5)	PPh_3(10)	MeOH / 70	67
4	NaO*t*Bu(5)	PCy_3(10)	MeOH / 70	90
5	NaO*t*Bu(10)	PCy_3(10)	MeOH / 70	92 [88]
6	NaO*t*Bu(15)	PCy_3(10)	MeOH / 70	95 [90]
7	NaO*t*Bu(15)	PCy_3(10)	tBuOH / 70	93
8	---	PCy_3(10)	MeOH / 70	7
9	NaO*t*Bu(5)	PCy_3(10)	MeOH / 25	19
10	NaO*t*Bu(5)	PCy_3(10)	THF[c] / 70	20
11	Cs_2CO_3(15)	PCy_3(5)	MeOH / 70	95

[a] Reaction conditions: **24a** (0.25 mmol), Bpin-NMe_2 (0.275 mmol), base (5-15 mol%), PR_3 (5-10 mol%), MeOH (2 mL), 70ºC, 17h. [b] Conversion calculated by G.C-MS on an average of two reactions. [c] THF (2 mL) + 2eq of MeOH added to the reaction.

Spectroscopic evidences have demonstrated the formation of the Lewis acid-base adduct [$RO^- \rightarrow$Bpin-NMe_2] (Scheme 5.13).



Scheme 5.13 *In situ* ^{11}B NMR of the suggested [RO$^-$→Bpin-NMe$_2$] adducts.

The original ^{11}B NMR spectrum of the aminoborane **36a,** in THF as solvent, shows a clear signal at 22.55 ppm which is typical of a sp^2 Bpin moiety bonded to an amino group. Upon addition of 1 eq of NaO*t*Bu, the signal shifted completely at higher fields (5.45 ppm), even at room temperature (Figure 5.3). No further changes were observed even in the presence of 2eq of MeOH at 60ºC. The new signal probably corresponds to the sp^3 Bpin moiety of the adduct [^{t}BuO$^-$→Bpin-NMe$_2$].

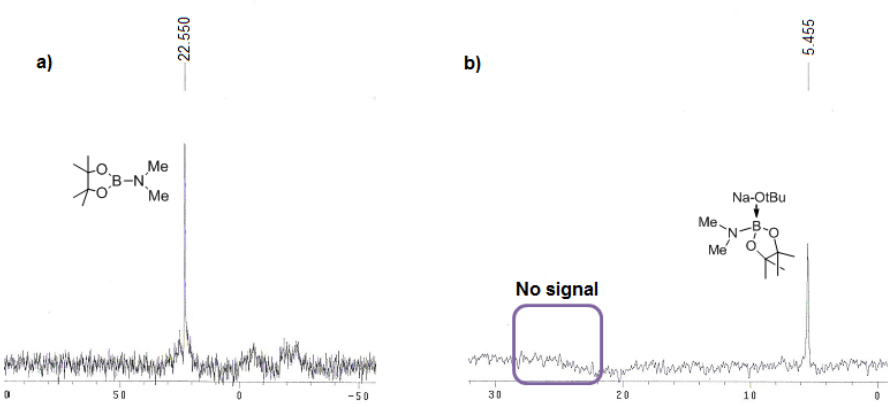


Figure 5.3 ^{11}B NMR spectra: a) Bpin(NMe$_2$) in THF at room temperature. b) 1 equivalent of Bpin(NMe$_2$) and 1 equivalent of NaOtBu in THF at room temperature.

However, when 1eq. of NaOMe was added to the THF solution of Bpin-NMe$_2$, the majority of the boron reagent remained unaffected, the signal at 22.55 ppm did not change significantly, and only a small signal appeared at 8.74 ppm (Figure 5.4).

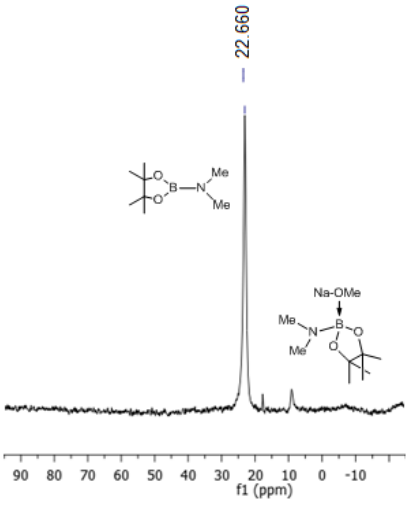


Figure 5.4 ^{11}B NMR spectrum of 1 equivalent of Bpin(NMe_2) and 1 equivalent of NaOMe in THF.

The equilibrium towards the free aminoborane was established when heating at 60ºC, the small signal dissapeared showing the original sp^2 Bpin signal. However, when 2eq. of MeOH were added, a total shift was observed towards the unique signal at 8.74 ppm, both at room temperature and 60ºC (Figure 5.5).

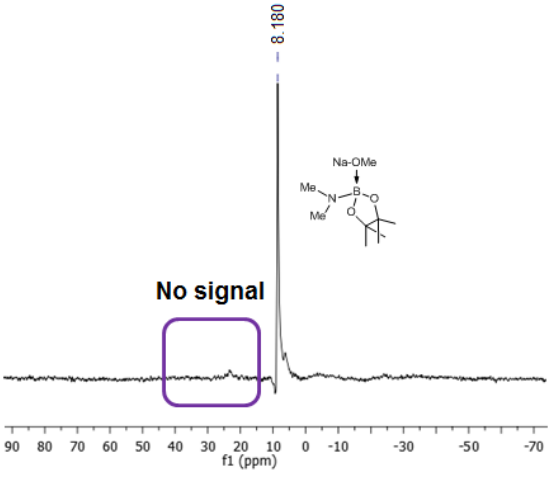
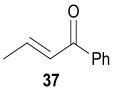
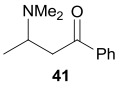
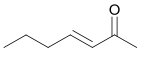
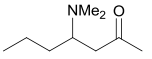
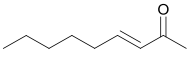
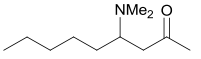
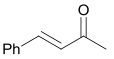
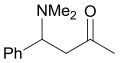
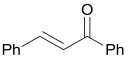
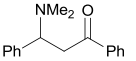
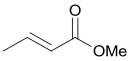
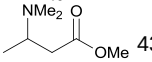
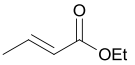
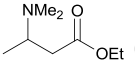
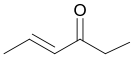
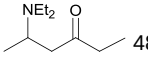
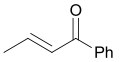
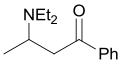


Figure 5.5 ^{11}B NMR spectrum of 1 equivalent of Bpin(NMe_2), 1 equivalent of NaOMe and 2 equivalent of MeOH in THF.

The scope of substrates towards the preparation of β-dimethylamino carbonyl compounds was examined next. As shown in Table 5.2, the substrate *trans*-1-phenyl-2-buten-1-one (**37**) was quantitatively converted into the corresponding β-dimethylamino ketone **41** (Table 5.2, entry 1), however the aliphatic ketones 3-hepten-2-one (**25a**) and 3-nonen-2-one (**14a**) were only moderately transformed into the β-amino ketones **42** and **43**, respectively, as a consequence of the bulkier alkyl C_β substituents (Table 5.2, entries 2 and 3). The least efficient β-amination reactions were observed in the case of the chalcones **1a** and **4a** (Table 5.2, entries 4 and 5). It seems that steric and electronic effects of the phenyl substituent on C_β diminished the nucleophilic attack of the activated aminoborane. Next, we turned our attention to explore the β-amination of the α,β-unsaturated esters methylcrotonate (**38**) and ethylcrotonate (**39**). In both cases the conversion was only moderate into the desired products (Table 5.2, entries 6-7). We also extended the organocatalytic addition of the diethylamino moiety when the aminoborane involved in the reaction was the analogue Bpin-NEt_2 (**36b**). By activation of **36b** with MeOH and base, the diethylamino moiety became nucleophilic enough to β-aminate substrates **24a** and **37**, and we were able to isolate the corresponding β-diethylamino ketones in moderate yields (Table 5.2, entries 8-9). This fact seems to be related with the less accentuated nucleophilic character of NEt_2 moiety in [RO^-→Bpin-NEt_2] versus [RO^-→Bpin-NMe_2].

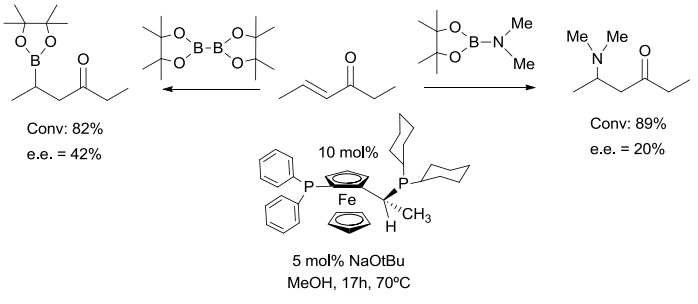
Table 5.2. β-Amination of α,β-unsatuarated substrates with Bpin-NMe_2 (**36a**) and Bpin-NEt_2 (**36b**) [a].

Entry	Substrate	Aminoborane Reagent	Product	Conv(%)[b] [*I.Y.*(%)]
1	 **37**	Bpin-NMe_2	 **41**	93[84]
2	 **25a**	„	 **42**	75[68]
3	 **14a**	„	 **43**	70[65]
4	 **1a**	„	 **44**	20
5	 **4a**	„	 **45**	25
6	 **38**	„	 **46**	43[37]
7	 **39**	„	 **47**	63[58]
8	 **24a**	Bpin-NEt_2	 **40b**	48[27]
9	 **37**	Bpin-NEt_2	 **41b**	45[32]

[a] Reaction conditions: substrate (0.25 mmol), Bpin-NR_2 R=Me,Et (0.27 mmol), NaOtBu(15mol%), PCy_3(10mol%), MeOH (2 mL), 70ºC, 17h. [b] Conversion calculated by G.C.-MS from an average of two reactions.

As we have recently demostrated, [4a] chiral phosphines can induce considerable enantioselectivity in organocatalytic β-boration of α,β-unsaturated carbonyl compounds. In this work, we also considered this possibility and we conducted a parallel β-boration (with B_2pin_2) and β-amination (with Bpin-NMe_2) of the model substrate **24a**, in the presence of a Josiphos type ligand. Scheme 5.13 shows that, under optimized conditions, the asymmetric induction in the organocatalytic β-

amination is lower than the corresponding organocatalytic β-boration, probably due to the less hindered NMe_2 versus Bpin nucleophilic counterpart.

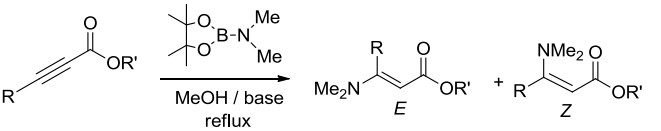


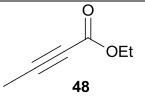
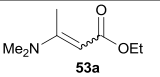
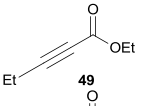
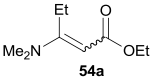
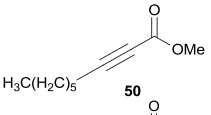
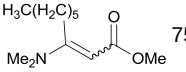
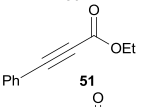
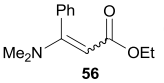
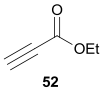
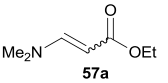
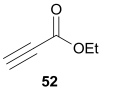
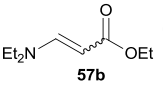
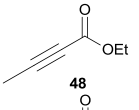
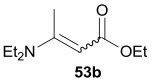
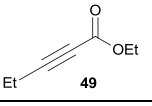
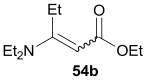
Scheme 5.13 Asymmetric β–amination reactions assisted by josiphos type ligand and compared with the corresponding β–boration reaction.

Next we explored the β-amination of the electron deficient α,β-ethylenic carbonyl substrates to find a direct methodology to form exclusively the *E* isomer of the corresponding β-enamino ester. Despite the interest in β-enamino derivatives, both as bioactive leads and as versatile building blocks, [17] their synthesis has been principally accomplished by the direct condensation of 1,3-dicarbonyl compounds with ammonia and primary amines. [18] Along these protocols, the *Z* isomer of the β-enamino ester was formed as the main product. However, when we performed the β-amination of ethyl-2-butynoate (**48**) and ethyl-2-pentynoate (**49**) with Bpin-NMe_2, the *E* isomer of the β-enamino ester was formed preferentialy (Table 5.3, entry 1-3).

In the case of substrates with bulkier substituents on C_β exclusive formation of the *E*-β-enamino ester has been observed (Table 5.3, entries 4,5). The total β-amination of the terminal α,β-ethylenic ester **51**, with Bpin-NMe_2 or Bpin-NEt_2 was complete in shorter reaction times (1h and 3h, respectively, Table 5.3, entries 6,7). Finally the selective formation of the *E*-β-enamino ester could also be observed in the diethylamino addition to ethyl-2-butynoate (**48**) and ethyl-2-pentynoate (**49**) (Table 5.3, entries 8,9).

Table 5.3. β-Amination of the electron deficient α,β-ethylenic carbonyl substrates with Bpin-NMe_2 (**36a**) and Bpin-NEt_2 (**36b**) [a].

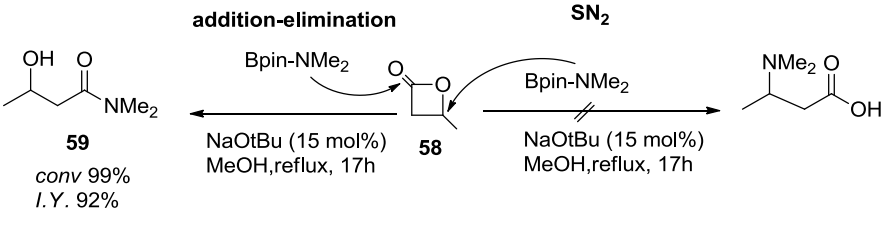


Entry	Substrate	Product	Conv(%)[b] [*I.Y.*(%)]	*E/Z* [c]
1[d]	 **48**	 **53a**	75	85/15
2			81[68]	84/16
3	 **49**	 **54a**	80[74]	88/12
4	 **50**	 **55**	75[63]	99/1
5	 **51**	 **56**	93[85]	99/1
6[e]	 **52**	 **57a**	99[93]	99/1
7[f]	 **52**	 **57b**	99[93]	99/1
8	 **48**	 **53b**	70[62]	99/1
9	 **49**	 **54b**	67[60]	99/1

[a] Reaction conditions: substrate (0.25 mmol), Bpin-NR_2 (1.5 eq), NaOtBu(25mol%), MeOH (2 mL), reflux, 17h. [b] Conversion calculated by G.C-MS on an average of two reactions. [c] *E/Z* ratio calculated from ^{1}H NMR spectroscopy. [d] NaO^{t}Bu(15mol%). [e] 1h. [f] 3h.

To complete this survey of amination through aminoboranes, we interested in studying the reactivity of Bpin-NMe_2 with γ-lactones, to elucidate the nucleophilic

character of the amino moiety in the adduct [RO^-→Bpin-NMe_2]. As it has been described,[19] hard nucleophiles express a strong preference for addition to the lactone carbonyl, providing ring opening via an addition–elimination pathway.[20] Alternatively, soft nucleophiles achieve better electronic matching with the electrophilic C_β, thereby promoting S_N2 displacement of the carboxylate group (Scheme 5.14). [21] When we performed the reaction of Bpin-NMe_2 with the β-butyrolactone (**58**) in MeOH-base media, the only product observed was the β-hydroxy N-dimethyl amide, by the activation of the carbonyl function as an evidence of the hard nucleophilic character of the amino moiety. This type of compounds have also been recently prepared from the copper [22a] or nickel [22b] catalyzed β-boration of α,β-unsaturated amides with B_2pin_2, followed by oxidation pathway. We were delighted to see that our novel organocatalytic approach provides the desired product in one step.



Scheme 5.14 Hypothetical reactivity of activated aminoboranes with β-butyrolactone **58**.

We demonstrated that the simple Lewis acid-base interaction of aminoboranes with alkoxides, forming in situ the adduct [RO^-→Bpin-NMe_2], seems to be the platform to enhance the nucleophilic attack of amino moieties towards electron deficinet olefins.

5.3 New route to synthesize amino alcohols

Following the previously described reactivity of the aminoboranes towards selective amination, we were able to synthesize different β–dimethyl or β–diethyl amino ketones and esters with high conversions. At this point, we considered the

possibility of performing the *in situ* reduction of the β–dimethylamino ketones to obtain the corresponding β–dimethyl aminoalcohols with a high *syn/anti* diastereomeric ratio, depending on the reducing agent involved. According to my previous experience in the reduction of (borylated) imines and ketones, the reducing agents BH_3·THF or $NaBH_4$ should easily reduce aminoketones with complete conversions and, probably, with high control of the diastereoselectivity. Having this information in mind, we carried out the reductions of the β–dimethyl ketones using these three reducing agents: BH_3·THF, $NaBH_4$ and DIBAL-H (Figure 5.6).

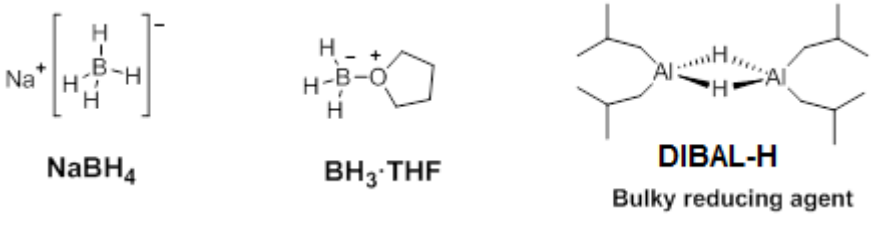
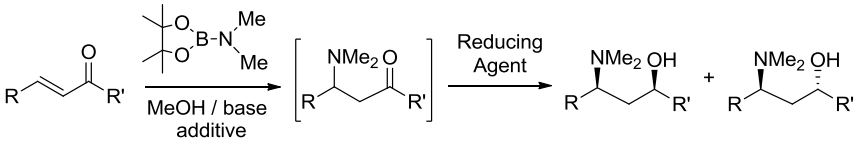
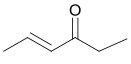
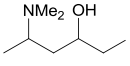
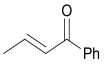
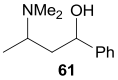
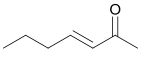
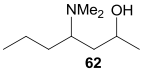
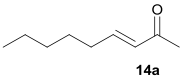
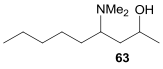


Figure 5.6 Reducing agents used in the β–dimethylamino ketone reduction.

When $NaBH_4$/MeOH was used, we obtained the *syn* β–dimethyl amino alcohol **60** in high diastereomeric ratio. The use of the DIBAL-H as reducing agent did not decrease significantly the diastereoselectivity but the BH_3·THF gave a close to 1:1 mixture of the two diastereoisomers (Table 5.4, entry 1). An different behavior was observed in the reduction of the β–dimetylamino ketone **41**, because the use of $NaBH_4$/MeOH provieded low dr but the *syn* diastereoisomer was the major isomer when BH_3·THF or DIBAL-H was involved (Table 5.4, entry 2). Similar behavior was observed with the reduction of β–dimethylamino ketones **42** and **43**, as DIBAL-H was poved to be the best reducing agent to control the formation of the *syn* diastereoisomer (Table 5.4, entry 3 and 4).

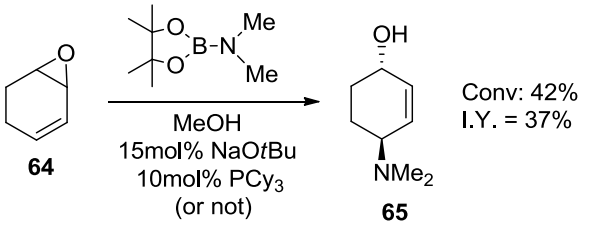
Table 5.4. Synthesis of γ-amino alcohols through β-dimethylamination with PinB-NMe_2 (**36a**) / reduction [a].



Entry	Substrate	Reducing Reagent	Product	Conv(%)[b] [*l.y.*(%)][d]	*Syn/anti* [c]
1	 **24a**	BH_3·THF	 **60**	95[92]	45/54
		DIBAL-H		70[65]	74/26
		$NaBH_4$		90[85]	93/7
2	 **37**	BH_3·THF	 **61**	93	72/28
		DIBAL-H		95[88]	85/15
		$NaBH_4$		90	56/44
3	 **25a**	BH_3·THF	 **62**	73	62/38
		DIBAL-H		75	70/30
		$NaBH_4$		75[62]	72/28
4	 **14a**	BH_3·THF	 **63**	78	67/33
		DIBAL-H		80	70/30
		$NaBH_4$		69[58]	62/38

[a] Reaction conditions: substrate (0.25 mmol), Bpin-NMe_2 (0.27 mmol), NaO*t*Bu(15mol%), PCy_3(10mol%), MeOH (2 mL), 70ºC, 17h. [b] Conversion calculated by G.C-MS from an average of two reactions. [c] dr calculated from ^{1}H NMR spectroscopy. [d] *Syn* diastereomer isolated.

Another way to obtain amino alcohols using the aminoboranes can be the amination ring-opening of cyclic vinyl epoxides via S_N2' from the adduct [RO^- →Bpin-NMe_2]. We carried out the β-amination with the 3,4-epoxy-1-cycohexene **64** using the optimal conditions found in the Table 5.1, in the absence of phosphines as additives. Therefore, exclusive formation of 1,4-cyclohexenyl dimethylamino alcohol **65** was observed (Scheme 5.15). Isolation and comparasion with reported NMR data for this polyfuntionalized compound [23] allowed us to characterize the compound as the *trans* isomer.



64 **65**

Scheme 5.15 Diastereoselective amination ring-opening of 3,4-epoxy-1-cyclohexene (**64**) with [RO^-→Bpin-NMe_2].

The amination ring-opening of cyclic vinyl epoxides seems to be a good method to obtain *trans* aminoalcohols and opens a new perspective towards the synthesis of amino alcohols.

5.4 Conclusions

In this chapter, we have studied the activation of aminoboranes towards the amination of activated olefins and β-lactones. The most relevant discoveries that we have made are:

- ✓ The simple Lewis acid-base interaction of aminoboranes with alkoxides, forming *in situ* the adduct $[RO^{-}\rightarrow B(OR)_2\text{-}N(R')_2]$, seems to be the platform to induce the nucleophilic attack of the amino groups towards α,β-unsaturated carbonyl compounds and cyclic vinyl epoxides.

- ✓ The addition of catalytic amounts of chiral phosphines to induce asymmetry has provided modest enantioselectivity in the C-N bond formation.

- ✓ Exclusive selectivity into the E isomer of the β-enamino esters formed from β-amination of deficient α,β-ethylenic carbonyl substrates demonstrated the preferential attack of the amino group in $[RO^{-}\rightarrow B(OR)_2\text{-}N(R')_2]$ to the C_β.

- ✓ The interaction of the alkoxide with the sp^2 Bpin moiety in the aminoborane can be followed by ^{11}B NMR spectroscopy and the subsequent enhancement of the nucleophilic character of the amino group has been proved after selecting the electrophilic reaction partner to elicit the mode of ring opening of β-butyrolactone, forming the β-hydroxy N-dimethyl amide exlusively.

- ✓ Following a simple one pot reaction, the 1,3- and 1,4-amino alcohols could be synthesized and isolated in moderate to high yield.

5.5 References

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Chapter 6: Conclusions

6.1 *Chapter 2:* Synthesis of enantioenriched β–boryl imines.

Initial attemps to transform C-B bond into C-N bonds with retention of configuration, were not successful. New strategy has been developed in this thesis, to accomplish the same target product formation. We proposed the β-boration of α,β–unsaturated imines, which has been carried out for the first time in this work.

Despite the fact that the synthesis of α,β–unsaturated imines was competitive with the aza-Michael conjugate addition, a series of α,β–unsaturated imines containing different electronic and steric properties, have been synthesized with high isolated yield.

The first copper-catalyzed β–boration of α,β–unsaturated imines has been developed under mild conditions. It is important to mention that high enantioselectivities (up to 99 e.e.%) have been induced in the formation of the new C-B bond using copper salts modified with chiral phosphine ligands. This methodology permits the synthesis of enantioenriched β–boryl imines that can be used as intermediates for the synthesis of chiral γ–amino alcohols.

Iron salts facilitated the β–boration of α,β–unsaturated imines with B_2pin_2 / base. From a mechanistic point of view Fe salts interact with the substrate, behaving as Lewis acid.

6.2 *Chapter 3:* One-pot routes to synthesize enantioenriched γ–amino alcohols.

We have established an asymmetric simple, one-pot, three-step synthetic route towards γ–amino alcohols consisting of β–boration/reduction/oxidation of α,β–unsaturated ketones. The first and key step is the enantioselective β–boration of

α,β–unsaturated imines. We identified several chiral phosphorus ligands which induce exceptional enantioselectivities on coordination to the copper catalytic system. Using achiral reducing agents for the reduction of C=N and C=O, we obtained total 1,3-diastereocontrol to *syn* or *anti*-isomer of γ–amino alcohol. The expertise on selective reducing reagents was provided by Prof. A. Whiting (Unversity of Durham).

The comparative study of catalytic β–boration/reduction/oxidation of α,β–unsaturated ketones and imines has highlighted two important features: an intramolecular B-N interaction could favour the *syn*-diastereoisomer formation and the asymmetric induction of the β–boration of α,β–unsaturated imines might be more successful than the corresponding α,β–unsaturated ketones. The substituents on the imine group seem to provide a beneficial effect on the enantioselection of the reaction.

An efficient one-pot 4-step protocol based on the *in situ* imine formation followed by copper catalysed β–boration/reduction/oxidation has been developed with the original ideas and collaboration of Prof. A. Whiting (University of Durham). This new one-pot step has circumvented the previous isolation of the α,β–unsaturated imines. In addition, a new catalytic Cu_2O-base free system was also discovered for the β–boration of α,β–unsaturated compounds. Excellent enantioselectivities are induced using cheap and no high-sensitive ligands, such as (*R*)-BINAP, upon coordination to Cu(I). Applying these new conditions of β–boration to the one-pot 4-step procedure, we have obtained γ–amino alcohols and we have generalized this methodology.

6.3 ***Chapter 4:*** Asymmetric metal free synthesis of β–amino alcohols.

The first organocatalytic nucleophilic addition of bis(pinacolato)diboron to tosylaldimines towards the synthesis of α–amino boronate esters have been

developed. The sole use of methanol, base and the diboron reagent were enough to form the catalytic system. The use of chiral phosphine as additives induced high enantioselectivities (*e.e.* up to 99%).

Taking into consideration the interesting applications of chiral β–amino alcohols, we have developed a direct, simple and efficient one-pot route based on the organocatalytic boron addition to tosylaldimines followed by homologation/oxidation sequences. The high enantiomeric excess induced in the organocatalytic boron addition (99 *e.e.*%) was preserved during the one-pot sequence to obtain the final desired chiral β–amino alcohol.

6.4 ***Chapter 5:*** Catalytic amination through boron chemistry

The simple Lewis acid-base interaction of aminoboranes with alkoxides, forming *in situ* the adduct $[RO^{-}\rightarrow B(OR)_2\text{-}N(R')_2]$, seems to be the platform to enhance the nucleophilic attack of amino moieties towards α,β-unsaturated carbonyl compounds and cyclic vinyl epoxides.

The addition of chiral phosphines to induce asymmetry has provided modest values of enantioselection in the C-N bond formation.

Exclusive selectivity into the *E* isomer of the β-enamino esters formed from β-amination of α,β-ethylenic carbonyl substrates demonstrated the preferential attack of the amino group from the adduct $[RO^{-}\rightarrow B(OR)_2\text{-}N(R')_2]$ to the C_β.

The interaction of the alkoxide with the sp^2 Bpin moiety in the aminoborane can be followed by ^{11}B NMR and the subsequent enhancement of the nucleophilic character of the amino group has been shown after selecting the electrophilic reaction partner to elicit the mode of ring opening of β-butyrolactone, forming the β-hydroxy N-dimethyl amide exlusively.

The β–amination of α,β–unsaturated ketones with aminoboranes followed by reduction of the C=O, using different reducing agents, have been designed as a

new one-pot sequence to synthesize 1,3-amino alcohols. In addition, the ring-opening of cyclic vinyl epoxides provides the 1,4-amino alcohols with moderate yields.

Chapter 7: Experimental Part

7.1 General considerations

All reactions and manipulations were carried out under argon atmosphere using Schlenk-type techniques. Solvents were dried using a solvent purification system (Pure SOLV system-4). Bis(pinacolato)diboron was used as purchased from AllyChem. Chiral ligand were kindly supplied by Solvias or DSM. All other materials were purchased directly from Sigma-Aldrich or Alfa-Aesar and used as received.

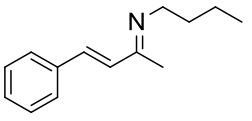
Deuterated solvents for routine NMR measurements were used as purchased from SDS or Cortecnet. NMR spectra were obtained using a Varian Mercury 400 spectrometer. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane and $CDCl_3$. $^{11}B\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to $BF_3{\cdot}OEt_2$ (δ $^{11}B\{^{1}H\}$ = 0.00 ppm) as the external reference. Coupling constants (*J*) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV or TOF detector. Chiralpak AD-H column (dimensions 250 × 4.6 mm), Chiralpak OD-H column (dimensions 250 x 4.6 mm) or Chiralpak IA-H column (dimensions 250 x 4.6 mm) were used. Electron impact (EI) (70 Ev) and chemical ionization (CI) were recorded with a Kratos MS50 or a Finnigan MAT 95S spectrometer. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer.

7.2 General methodology for the synthesis of the α,β–unsaturated imines [1]

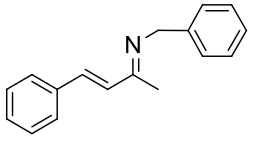
The amine (5 mmol), ketone (5 mmol), and montmorillonite K10 as catalyst and dehydrating agent (500 mg) were stirred in CH_3CN (5 mL) for 16 hour at room temperature. The solution was filtered through a pad of celite, and the product was isolated by removing all the volatiles (solvent, remaining amine and ketone) in vacuum, using a Kugelrohr apparatus.

7.3 Characterization of α,β–unsaturated imines:



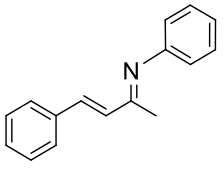
7.3.1 Synthesis of (E)-N-((E)-4-phenylbut-3-en-2-ylidene)butan-1-amine (1b)

Yield 73% (syn/anti=1:9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 1 H), 7.48-7.46 (m, 2H), 7.46 (d, *J* = 16.3 Hz, 1H), 7.33-7.32 (m, 2H), 6.67 (d, *J* = 16.3 Hz, 1H), 3.62 – 3.05 (t, *J* = 6.8 Hz, 2H), 2.25 (s 3H), 1.73 – 1.40 (m, 2H), 1.36 – 1.13 (m, 2H), 0.89 – 0.64 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz) δ 160.75, 130.42, 128.71, 128.55, 127.98, 127.11, 61.49, 51.92, 32.98, 20.45, 13.91; MS (70 eV) *m/z* : 202.15 [M^+].



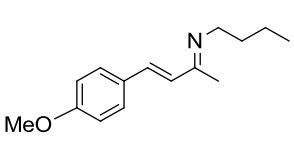
7.3.2Synthesisof (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine (1c)

Yield 89% (syn/anti = 3:7). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.50 – 7.26 (m, 10H), 7.01 (d, *J* = 16.8 Hz, 1H), 6.97 (d, *J* = 16.8, 1H), H), 4.76 (s, 1H), 4.60 (s, 1H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 67.5 MHz) δ 160.91, 139.54, 136.55, 133.09, 128.21, 126.65, 126.27, 126.01, 125.92, 125.70, 125.52, 125.40, 124.70, 124.49, 50.78, 12.04. MS (70 eV) *m/z* : 236.14 [M^+].



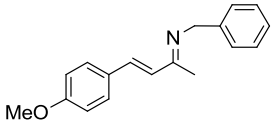
7.3.3 Synthesis of (*E*)-N-((*E*)-4-phenylbut-3-en-2-ylidene)aniline (1d)

Yield 78% (anti isomer). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.46 – 7.16 (m, 10H), 7.43 (d, *J* = 16 Hz, 1H), 6.64 (d, *J* = 16, 1H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 67.5 MHz) δ 166.38, 143.59, 134.46, 129.32, 129.09, 128.84, 128.45, 127.19, 126.44, 115.15, 113.81, 15.87. MS (70 eV) *m/z* : 222.30 [M^+].



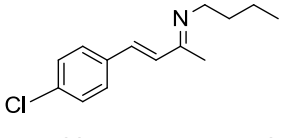
7.3.4 Synthesis of (*E*)-N-((*E*)-4-(4-methoxyphenyl)but-3-en-2-ylidene)butan-1-amine (2b)

Yield 95% (syn/anti = 2:8). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.48 (d, *J* = 8.8 Hz, 0.4H), 7.42 (d, *J* = 8.8 Hz, 1.6H), 6.97-6.90 (m, 1H), 6.89-6.84 (m, 4H), 6.76 (d, *J* = 16.4 Hz, 0.8H), 6.56 (d, *J* = 16.4 Hz, 0.2H), 3.8 (s, 0.6H), 3.78 (s, 2.4H), 3.52 (t, *J* = 14.4 Hz, 0.4H), 3.40 (t, *J* = 14.4 Hz, 1.6H), 2.12 (s, 0.6H), 2.02 (s, 2.4H); 1.72-1.62 (m, 2H), 1.44-1.62 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 165.69, 159.92, 143.25, 134.21, 130.76, 130.03, 129.11, 128.41, 127.98, 117.33, 114.28, 55.95, 55.24, 51.54, 50.63, 33.06, 27.44, 24.24, 20.97, 14.05, 13.37. MS (70 eV) *m/z* : 232.16 [M^+].



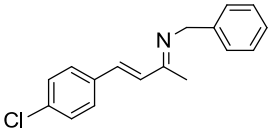
7.3.5 Synthesis of (*E*)-N-((*E*)-4-(4-methoxyphenyl)but-3-en-2-ylidene)-1 phenylmethanamine (2c)

Yield 91% (syn/anti = 2:8).^{1}H NMR ($CDCl_3$, 400MHz) δ 7.37 (d, *J* = 8.8 Hz, 1.6H), 7.28-7.16 (m, 5H), 6.96 (d, *J* = 8.8 Hz, 0.4H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.69 (s, 0.4H), 4.57 (s, 1.6H), 3.74 (s, 0.6H), 3.72 (s, 2.4H), 2.27 (s, 0.6H), 2.07 (s, 2.4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 166.83, 160.08, 134.65, 130.70, 129.98, 128.95, 128.52, 128.29, 127.92, 127.08, 126.79, 126.67, 114.32, 55.93, 55.31, 14.00. MS (70 eV) *m/z* : 266.15 [M^+].



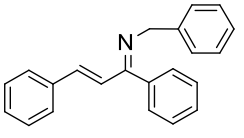
7.3.6 Synthesis of (*E*)-N-((*E*)-4-(4-chlorophenyl)but-3-en-2-ylidene)butan-1-amine (3b)

Yield 73% (syn/anti = 2:8). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 0.50H), 7.29 (d, *J* = 8.4 Hz, 0.50H), 7.01 (d, *J* = 16.8 Hz, 1.2H), 6.98 (d, *J* = 16.8 Hz, 1.2H), 3.55 (t, *J* = 7.6 Hz, 0.50H), 3.44 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 0.75H), 2.06 (s, 3H); 1.76-1.63 (m, 2.5H), 1.47-1.37 (m, 2H), 1.30-1.25 (m, 0.5H), 0.98 (t, *J* = 7.2 Hz, 3.8H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 165.26, 141.98, 129.38, 129.22, 128.97, 128.23, 128.32, 127.43, 51.88, 33.18, 30.86, 20.76, 14.01. MS (70 eV) *m/z*: 236.11 [M^+].



7.3.7 Synthesisof(*E*)-N-((*E*)-4-(4-chlorophenyl)but-3-en-2-ylidene)-1-phenylmethanamine (3c)

Yiel 73% (syn/anti = 2:8). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.36-7.31 (m, 5H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 16.4, 1H), 6.98 (d, *J* = 16.4, 1H), 4.79 (s, 0.4H), 4.67 (s, 1.6H), 2.40 (s, 0.5H), 2.18 (s, 2.5H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 166.69, 140.15, 134.68, 133.10, 129.01, 128.55, 128.32, 127.89, 127.82, 126.78, 125.93, 56.00, 14.22. MS (70 eV) *m/z* : 270.09 [M^+].



7.3.8 Synthesisof(*Z*)-N-((E)-1,3-diphenylallylidene)-1-phenylmethanamine (4c) [2]

Yield 43% (syn/anti = 2:8).^{1}H NMR ($CDCl_3$, 400MHz) δ 7.29-7.23 (m, 5H), 7.19-7.17 (m, 5H), 7.11-6.97 (m, 6H), 6.64 (d, *J* = 16.4, 0.2H), 6.29 (d, *J* = 16.4, 0.8H), 4.72 (s, 0.4H), 4.25 (s, 1.6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 170.33, 140.52, 140.00, 136.11, 135.89, 132.61, 128.87, 128.65, 128.21, 127.75, 127.30, 16.83, 57.55, 55.73. MS (70 eV) *m/z* : 298.15 [M^+].

7.4 Experimental procedure for the iron-catalyzed asymmetric β–boration of α,β–unsaturated imines with bis(pinacolato)diboron

Iron complexes (0.01 mmol of metal) and phosphine (0.02 mmol) were placed in a schlenck and dissolved with THF (1.5 mL) under nitrogen. 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 (5 mol%) was added, and the mixture was allowed to stir at 70ºCoil 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 concentrated on a rotary evaporator and analyzed by ^{1}H-NMR to determine the conversion.

7.5 Experimental procedure for the copper(I)-phosphine catalyzed β–boration of α,β–unsaturated ketones and imines with bis(pinacolato)diboron

PPh_3 (5.35 mg, 0.02 mmol), NaO*t*Bu (1.47 mg, 0.015 mmol) and CuCl (1 mg, 0.01 mmol) were transferred into an oven-dried Schlenk tube and dry THF (2 mL) was added under argon. The mixture was stirred for 30 minutes at room temperature to form the catalyst precursor. Bis(pinacolato)diboron (140 mg, 0.55 mmol) was added and the solution was stirred for 5 minutes. Then, the α,β–unsaturated ketone or imine (0.5 mmol) dissolved in THF (0.5 mL) and MeOH (40 µl, 1 mmol) were added successively. The reaction mixture was stirred for 6 hours at room temperature. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine conversion and selectivity. The products were purified using flash chromatography.

7.6 Experimental procedure for the copper(I)-phosphine catalyzed asymmetric β–boration of α,β–unsaturated imines with bis(pinacolato)diboron

Stock solutions of the CuOTf, the chiral ligands, and the α,β–unsaturated imines were prepared in the following way. Cu(OTf) (0.04 mmol) was dissolved in dry THF (1 mL). Stock solution of each chiral ligand (0.032 mmol for monodentate or 0.016 for bidentate) was prepared in dry THF (2.8 mL). Stock solution of each imines (2 mmol) were prepared in THF (2 mL). NaO*t*Bu (0.018 mmol, 9 mol %) stock solution of CuOTf (100 µl), and stock solution of the chiral ligand (700 µl) were transferred into Schlenk tube under nitrogen. The suspension was stirred for 10 minutes and bis(pinacolato)diboron (58 mg, 0.22 mmol) was added. The suspension was stirred for 5 minutes. Stock solution of the substrate (200 µl, 0.2 mmol) and MeOH (16 µl, 2eq.) were added, and the mixture was allowed to stir at room temperature. After 6 h, an aliquot of the solution (100 µl) was taken and

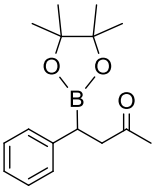
analyzed used by ^{1}H NMR to determine conversion and by HPLC-UV to determine directly the enantiomeric excess.

7.7 Screening of chiral ligands for the asymmetric Cu_2O/L catalyzed β–boration of α,β–unsaturated imines formed *in situ*

Cu_2O (3 mol%, 0.0075 mmol, 1 mg), chiral diphosphine (6 mol%, 0.015 mmol) and THF (1 mL) were transferred into a Radley's Carousel 12 place reactor under Ar. The mixture was stirred for 15 min at room temperature. Bis(pinacolato)diboron (0.28 mmol, 70 mg, 1.1 equiv.) was added and the solution was stirred for 10 min. Then benzylamine (0.25 mmol, 27 µl, 1 equiv.) and the α,β–unsaturated ketone (0.25 mmol) were added simultaneously, followed by the addition of MeOH(0.55 mmol, 25 µl, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the conversion towards the desired β–boryl imine products. The enantiomeric excess were determined directly by HPLC-UV or by HPLC-MS from the corresponding β–boryl ketone derivative obtained by hydrolysis.

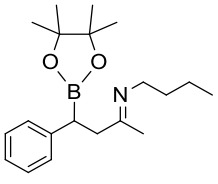
The hydrolysis protocol: To determine enantiomeric excesses of the β–borated products, some of the β–boryl imines obtained in the above procedures were converted into the corresponding β–boryl ketones following the procedure: Distillated water (1 mL) was added to the crude reaction product (cc. 0.25 mmol) in THF (1 mL). The reaction mixture was stirred vigorously for 2 h at RT. Then diluted with dichloromethane and extracted (3 x 2 mL). The combined organic phases were dried over Mg_2SO_4 and concentrated. The β–boryl ketones derived were dissolved in isopropanol solvent and analysed by chiral HPLC-MS to determine the enantiomeric excess.

7.8 Characterization of β–boryl ketones and imines:



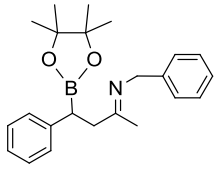
7.8.1. Synthesis of 4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one (5a) [3]

Yield 42%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.20 (m, 5H), 3.08 (dd, *J* = 18.4, 10.8 Hz, 1H), 2.87 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.66 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.18 (s, 3H), 1.22 (s, 6H), 1.16 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 208.5, 141.8, 128.6, 128.3, 125.6, 83.5, 47.6, 29.7, 24.6. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 37.02.



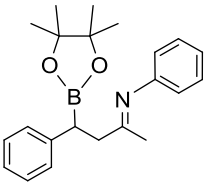
7.8.2 Synthesis of (*E*)-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)butan-1-amine (5b)

Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.19 (m, 5H), 3.54 (t, *J* = 8 Hz, 2H), 3.03 (dd, *J* = 20, 8 Hz, 1H), 2.81 (dd, *J* = 20, 8 Hz, 1H), 2.65 (m, 1H), 2.18 (s, 3H), 1.43 (m, 4H), 1.24 (s, 6H), 1.18 (s, 6H), 0.88 (t, *J* = 8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 160.99, 134.62, 129.00, 128.35, 127.07, 87.76, 61.72, 52.15, 32.70, 29.73, 27.79, 21.21, 13.98. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.72. MS (70 eV) *m/z* : 330.28 [M^+].



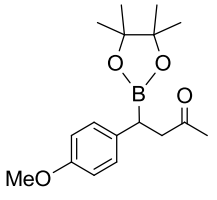
7.8.3 Synthesis of (*E*)-1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine (5c)

Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.07 (m, 10H), 4.80 (d, *J* = 15 Hz, 1H), 4.65 (d, *J* = 15 Hz, 1H), 3.03 (dd, *J* = 20, 8 Hz, 1H), 2.77 (dd, *J* = 20, 8 Hz, 1H), 2.25 (m, 1H), 2.10 (s, 3H), 1.19 (s, 6H), 1.13(s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 167.90, 139.54, 136.63, 136.24, 132.94, 128.37, 126.65, 126.34, 125.7, 88.16, 51.19, 36.72, 29.40, 22.17, 13.25. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.18. MS (70 eV) *m/z* : 364.30 [M^+].



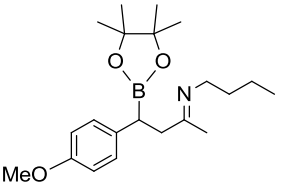
7.8.4. Synthesis of (*E*)-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)anilina (5d)

Yield 29 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 10H), 2.91 (dd, *J* = 20, 8 Hz, 1H), 2.64 (dd, *J* = 20, 8 Hz, 1H), 2.50 (m, 1H), 2.19 (s, 3H), 1.32 (s, 6H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.99, 148.93, 145.35, 132.77, 132.42, 131.39, 131.08, 130.11, 129.46, 87.27, 52.63, 29.53, 25.62, 19.67; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 21.38; MS (70 eV) *m/z* : 350.27 [M^+].



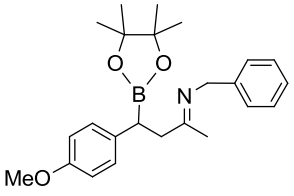
7.8.5 Synthesis of 4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one (6a)[4]

Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 6.8 Hz, d), 6.80 (d, *J* = 6.8 Hz, d), 3.75 (s, 3H), 3.00 (dd, *J* = 18, 10.8 Hz, 1H), 2.82 (dd, *J* = 18, 5.2 Hz, 1H), 2.58 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.11 (s, 3H), 1.21 (s, 6H), 1.15 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 208.56, 157.53, 133.53, 129.09, 114.42, 113.89, 83.33, 60.39, 55.16, 47.81, 29.63, 24.52, 24.49. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.62. MS (70 eV) *m/z* : 305.18 [M^+].



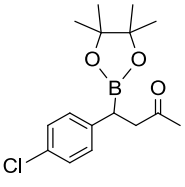
7.8.6 Synthesis of (*E*)-N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)butan-1-amine (6b)

Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 3.69 (s, 3H), 3.48 (t, *J* = 10 Hz, 2H), 2.97 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.65 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.10 (s, 3H), 2.06 (t, *J* = 8.4 Hz, 1H), 1.37-1.27 (m, 2H), 1.20-1.17 (m, 2H), 0.97 (s, 6H), 0.91(t, *J* = 7.2 Hz, 3H) 0.85 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 185.62, 156.43, 139.29, 128.58, 113.99, 79.11, 55.24, 45.88, 31.07, 26.47, 24.48, 21.03, 18.26, 13.91. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 20.21. MS (70 eV) *m/z* : 360.26 [M^+].



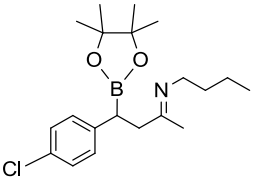
7.8.7 Synthesis of (*E*)-N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (6c)

Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.67 (d, *J* = 14.8 Hz, 1H), 3.03 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.74 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.20 (t, *J* = 8 Hz,1H), 1.93 (s, 3H), 0.95 (s, 6H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.53, 155.40, 139.07, 135.92, 129.11, 128.77, 127.75, 127.41, 113.90, 113.31, 79.64, 55.23, 49.55, 46.78, 27.17, 26.72, 24.48, 19.25. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 19.21. MS (70 eV) *m/z* : 394.25 [M^+].



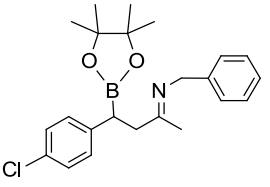
7.8.8 Synthesisof4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one (7a)

Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8 Hz, d), 7.09 (d, *J* = 8 Hz, d), 2.94 (dd, *J* = 18.4, 10 Hz, 1H), 2.78 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.56 (dd, *J* = 10, 5.6 Hz, 1H), 2.07 (s, 3H), 1.15 (s, 6H), 1.09 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 208.28, 140.48, 129.76, 128.78, 124.11, 83.86, 60.72, 47.48, 29.83, 24.80, 24.74. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.16; MS (70 eV) *m/z*: 309.14 [M^+].



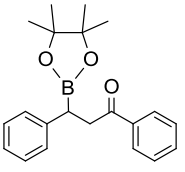
7.8.9 Synthesis of (*E*)-N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)butan-1-amine (7b)

Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.4 ,2H), 6.97 (d, *J* = 8.4, 2H), 3.48 (t, *J* = 7.2 Hz, 2H), 2.98 (dd, *J* = 19.6, 8Hz, 1H), 2.64 (dd, *J* = 19.6, 7.6 Hz, 1H), 2.28 (t, *J* = 8 Hz, 1H), 2.09 (s, 3H), 2.08 (m, 1H), 1.76-1.54 (m, 2H), 1.36-1.28 (m, 2H), 0.97 (s, 6H), 0.91 (t, *J* = 7.2 Hz,3H), 0.84 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 185.45, 145.43, 129.47, 129.22, 128.51, 127.53, 79.24, 46.22, 31.51, 27.21, 26.48, 24.57, 20.68, 18.04, 13.75. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 18.99; MS (70 eV) *m/z* : 380.25 [M^+].



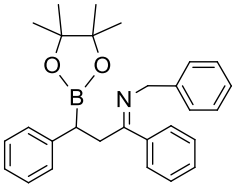
7.8.10 Synthesis of (*E*)-N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2 dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (7c)

Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.11 (d, *J* = 8.4 ,2H), 7.05 (d, *J* = 8.4, 2H), 4.84 (d, *J* = 15.2 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 3.09 (dd, *J* = 20.4, 8 Hz, 1H), 2.78 (dd, *J* = 20.4, 8 Hz, 1H), 2.28 (t, *J* = 8 Hz, 1H), 2.02 (s, 3H), 0.99 (s, 6H), 0.89 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 189.36, 149.13, 135.69, 129.52, 129.18, 128.79, 128.51, 127.68, 127.58, 127.46, 79.41, 49.56, 46.22, 27.55, 26.44, 24.49, 19.45. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 18.93. MS (70 eV) *m/z* : 398.19 [M^+].



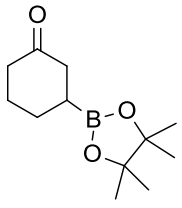
7.8.11 Synthesis of 1,3-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (8a)[5]

Yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.97 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.31−7.15 (m, 5H), 3.56 (dd, *J* = 18.3 Hz, 10.8 Hz, 1H), 3.43 (dd, *J* = 18.3 Hz, 5.4 Hz, 1H), 2.80 (dd, *J* = 10.8 Hz, 5.1 Hz, 1H), 1.25 (s, 6H), 1.17 (s, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ 199.81, 142.03, 136.87, 133.23, 128.61, 128.66, 128.59, 128.21, 125.72, 83.53, 43.39, 24.72, 24.63; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 34.08..



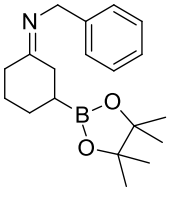
7.8.12 Synthesisof(*Z*)-N-(1,3-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propylidene)-1-phenylmethanamine (Z)-N-((E)-1,3-diphenylallylidene)-1-phenylmethanamine(8c)

Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.44-7.04 (m, 13H), 4.85 (d, *J* = 15.2 Hz, 1H), 4.71 (d, *J* = 15.2 Hz, 1H), 3.34 (dd, *J* = 15.2, 8 Hz, 1H), 3.13 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.48 (t, *J* = 8 Hz, 1H), 1.08 (s, 6H), 0.958 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 173.84, 141.79, 138.24, 134.88, 132.69, 130.58, 128.95, 128.62, 128.46, 128.35, 128.03, 127.99, 125.32, 83.02, 57.46, 43.22, 35.30, 24.79, 24.09. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 18.10. MS (70 eV) *m/z* : 426.25 [M^+].



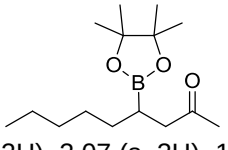
7.8.13 Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone (15a) [6]

Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33-2.18 (m, 4H), 2.04-1.96 (m, 1H), 1.84-1.77 (m, 1H), 1.73-1.62 (m, 1H), 1.60-1.51 (m, 1H), 1.42-1.34 (m, 1H), 1.17 (s, 12H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ 212.25, 83.41, 42.52, 41.82, 28.38, 26.45, 24.69, 24.65.^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.41. MS (70 eV) *m/z* : 225.16 [M^+].



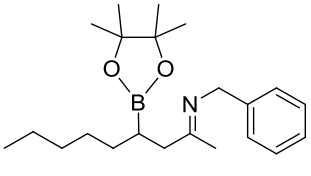
7.8.14 Synthesis of (S,Z)-1-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexylidene)methanamine (15c)

Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 – 7.20 (m, 5H), 4.59 (m, 2H), 2.35 – 2.17 (m, 4H), 1.72 – 1.51 (m, 2H), 1.69 – 1.49 (m, 2H), 1.45 – 1.29 (m, 1H), 1.24 (s, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 54.82, 48.85, 43.70, 26.77, 24.84, 24.69, 17.60;^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 22.15. MS m/z (ESI+) 314.24 (M+1) .



7.8.15. Synthesis of 1, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-one (16a) [6]

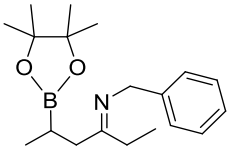
Yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (d, *J* = 7.2 Hz, 2H), 2.07 (s, 3H), 1.28-1.21 (m, 9H), 1.20 (s, 6H), 1.08 (s, 6H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 209.2, 82.9, 45.8, 31.9, 30.3, 29.6, 28.5, 24.9, 24.7, 24.6, 22.5, 14.00. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 38.12.



7.8.16 Synthesis of (*E*)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-ylidene)methanamine (16c)

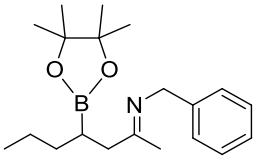
Yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 4H), 7.18-7.16 (m, 1H), 4.71 (d, *J* = 15.2 Hz, 1H), 4.59 (d, *J* = 15.2 Hz, 1H), 2.74 (dd, *J* = 19.7, 8.0 Hz, 1H), 2.46 (t, *J* = 6.6 Hz, 1H), 2.26 (dd, *J* = 19.7, 3.5 Hz, 1H), 1.81 (s, 3H), 1.63-1.56 (m, 2H), 1.29-1.18 (m, 6H), 1.14 (s, 6H), 1.10 (s, 6H),

0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ189.79, 143.25, 136.27, 128.63, 128.50, 128.35, 128.14, 128.01, 127.55, 127.15, 127.03, 126.87, 126.75, 79.03, 46.49, 32.13, 29.66, 27.02, 25.28, 24.73, 22.81, 19.28, 14.18; ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 14.26. MS m/z (ESI+) 357.20 (M+1)



7.8.17 Synthesis of (*E*)-1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine (26c)

Yield 35%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.05 (m, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 4.58 (d, *J* = 15.2 Hz, 1H), 2.93 (dd, *J* = 22.4, 6.8 Hz 1H), 2.47 (t, *J* = 7.6 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 2.09 (dd, *J* = 22.4, 3.5 Hz, 1H), 1.25 (d, *J* = 7.6 Hz, 3H), 1.13(s, 6H), 1.09 (s, 6H), 0.81 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 48.85, 43.70, 26.77, 24.84, 17.60, 9.26. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 13.83.MS m/z (ESI+) 316.25 (M+1).



7.8.18 Synthesis of (*E*)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-ylidene)methanamine (27c)

Yield 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.29 – 7.23 (m, 4H), 7.18 – 7.15 (m, 1H), 4.71 (d, *J* = 15.2 Hz, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 2.74 (m, 1H), 2.48 (t, *J* = 6.6 Hz, 1H), 2.19 (dd, *J* = 19.7, 3.5 Hz, 1H), 1.84 (s, 3H), 1.52-1.34 (m, 2H), 1.29-1.23 (m, 2H), 1.13 (s, 6H), 1.10 (s, 6H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.86, 143.18, 136.25, 128.64, 128.52, 128.36, 128.15, 128.01, 127.54, 127.16, 127.05, 126.78, 79.05, 46.46, 34.43, 27.00, 26.42, 24.83, 22.83, 19.29, 14.36.^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 13.99.MS m/z (ESI+) 329.25 (M+1).

7.9 Experimental procedure for 1,3-difunctionalization *via* reduction of the β–boryl ketones and imines, followed by C-Bpin oxidation

To a stirred solution of the β–imino or ketone boronate ester (0.5 mmol) in dry THF (5 ml), at the temperature specified in **7.9.1.-7.9.4.**, the reducing agent (1.5 mmol) was slowly added under argon. After the reaction time specified in **7.9.1.-7.9.4.**, the solution was cooled to 0 ºC, and treated with NaOH (aq.) (10 mL of a 1.0 M solution, 10 mmol) and H_2O_2 (aq.) (750 µl of a 30% w/v solution, 7.65 mmol). After 3 hours vigorous stirring yielded a colorless solution. This solution was partitioned between ethyl acetate and saturated NaCl (aq.). The combined organic phases were dried, and the solution was concentrated in vacuum. The obtained cloudy oil was analyzed directly by ^{1}H-NMR to determine conversion and the diastereoselectivity.

7.9.1 Reduction with BH_3·THF

BH_3·THF (1 M) (1.5 mL, 1.5 mmol) was added dropwise to a stirred solution of the β–iminoboronateester (0.5 mmol) in THF (5 mL) at 0°C. The reaction mixture was left to warm up to room temperature while constant stirring for 15 hours.

7.9.2 Reduction with $NaBH_4$

The β–iminoboronate ester (0.5 mmol) was dissolved in EtOH, MeOH or wet THF (2 v/v% H_2O) (5mL), and the solution was cooled to -50 ºC. $NaBH_4$ (58 mg, 1.5 mmol) was added to the solution, and the reaction mixture left to warm up to room temperature while constant stirring for 3 hours.

7.9.3 Reduction with DIBAL-H

DIBAL-H (1M in toluene) (1.5 mL, 1.5 mmol) was added dropwise to a THF solution of β–iminoboronate ester (0.5 mmol in 5 mL) at -78ºC. The reaction was

stirred for 2 hours at -78 ºC. The cooling bath was removed, and the reaction mixture was stirred overnight.

7.9.4 Reduction with DIBAL-H, $ZnCl_2$

DIBALH (1M in toluene) (1.5 mL, 1.5 mmol) was added dropwise to a solution of β–iminoboronate ester (0.5 mmol) and $ZnCl_2$ (355 mg, 1 mmol) in THF (5 mL) at -78ºC. The reaction was stirred for 2hours at -78 ºC. The cooling bath was removed, and the reaction mixture was stirred overnight.

7.10 One-pot copper-catalyzed asymmetric β-boration / reduction / oxidation of α,β–unsaturated ketones and imines

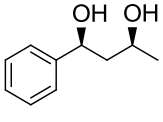
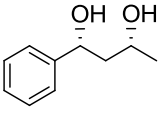
CuOTf (0.01 mmol), phosphorus ligand (0.01 mmol when diphosphine, or 0.02 mmol when monodentate phosphoramidite) and Na*t*OBu (0.03 mmol) were transferred into a Schlenk tube, and dissolved in THF (1.5 mL) under nitrogen. The suspension was stirred for 10 minutes and bis(pinacolato)diboron (140 mg, 0.55 mmol) was added. The suspension was stirred for 5 minutes. A solution of the corresponding α,β-unsaturated imine or ketone (0.5 mmol) was then added in 1 mL of THF. Finally, MeOH (40 µl, 1 mmol, 2 eq.) was added, and the mixture was allowed to stir at room temperature for 6-12h.

According to the reduction procedures described in **6.9**, the reaction mixture was cooled to low temperatures, and the reducing agent (1.5 mmol) was added *in situ*. The solution was treated with NaOH (aq.) (5 mL of a 1.0 M solution, 5 mmol) and H_2O_2 (aq.) (500 µl of a 30% w/v solution, *ca.* 4 mmol). Heating the mixture at reflux for 1 hour resulted in a colorless solution. This solution was partitioned between ethyl acetate and saturated NaCl (aq.). The organic phase was dried over $MgSO_4$. Evaporation of the organic solvents yielded the crude products as cloudy oils. They were analyzed directly by ^{1}H NMR to calculate the conversions, and by HPLC-UV or HPLC-MS to determine directly the enantioselectivities and diastereoselectivities.

7.11 One pot Cu_2O/(*R*)-BINAP catalyzed β-boration / reduction / oxidation of α,β–unsaturated imines formed *in situ*

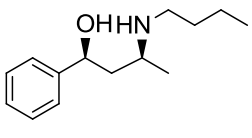
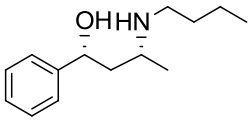
Copper(I) salts (1.5-3 mol%), (*R*)-BINAP ligand (3-6 mol%, 0.0075-0.015 mmol, 4.7-9.3 mg), were transferred into a Schlenk tube and dissolved in THF (1 mL) under Ar. After 15 min, bis(pinacolato)diboron (70 mg, 0.28 mmol, 1.1 equiv.) was added to the solution and stirred during 10 min. Then benzylamine (0.25mmol, 27 µl) and α,β–unsaturated ketone (0.25 mmol) were added at the same time, followed by the addition of MeOH (0.55 mmol, 25 µl, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The reaction products and conversion to the desired β–boryl imine was determined by ^{1}H NMR and the enantiomeric excess was determined directly by HPLC-UV.

7.12 Characterization of γ–amino alcohols and 1,3-diols:

7.12.1 (*syn*)-1-phenylbutane-1,3-diol (9a) [7]

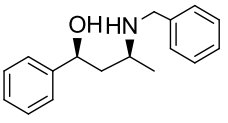
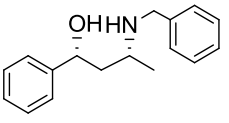
Yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.25 (m, 5H), 4.83 (dd, *J* = 10, 3.2 Hz, 1H), 4.07 (m, 1H), 1.79 (dt, *J* = 14.8, 10 Hz, 1H), 1.67 (dt, *J* = 14.8, 3.2 Hz, 1H), 1.29 (d, *J* = 6.4Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 148.79, 128.43, 127.41, 125.53, 70.57, 68.70, 47.05, 19.03. MS (70 eV) *m/z* : 167.09 [M^+].

7.12.2 (*syn*)-(butylamino)-1-phenylbutan-1-ol (9b)

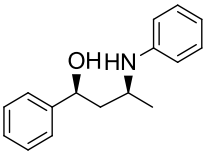
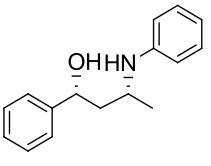
Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 5H), 4.95 (dd, *J* = 11.2, 2 Hz, 1H), 3.04 (m, 1H), 2.84 (m, 1H), 2.57 (m, 1H), 1.71 (dt, *J* = 14.4, 2 Hz, 1H), 1.57-1.48 (m, 3H), 1.43-1.38 (m, 2H), 1.17 (d, *J* = 6.4Hz, 3H), 0.96 (t, *J* = 6Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 142.32, 128.35, 127.46, 125.74, 74.13, 55.15, 50.85, 44.40, 30.589, 20.74, 19.99, 14.01. MS (70 eV) *m/z*: 238.21 [M^+].

7.12.3 (*syn*)-(benzylamino)-1-phenylbutan-1-ol (9c)

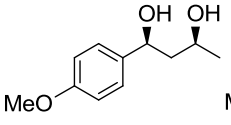
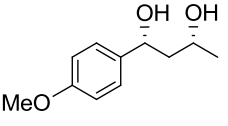
Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H), 4.97 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.03 (d, *J* = 12 Hz, 1H), 3.82 (d, *J* = 12 Hz, 1H), 3.15-3.11 (m, 1H), 1.78 (td, *J* = 14.4, 2.4 Hz, 1H), 1.64 (td, *J* = 14.4, 10.8 Hz, 1H), 1.25 (d, *J* = 6Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 145.23, 139.28, 128.62, 128.39, 128.21, 128.16, 127.34, 126.95, 125.55, 74.95, 54.30, 50.87, 46.01, 21.02. MS (70 eV) *m/z* : 288.22 [M^+].

7.12.4 (*syn*)-1-phenyl-3-(phenylamino)butan-1-ol (9d)

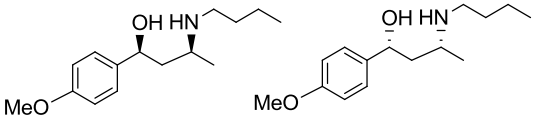



Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2 Hz, 2H), 7.32-7.28 (m, 4H), 7.19 (t, *J* = 8.4 Hz, 1H), 6.79 (t, *J* = 6.4 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 2H), 4.98 (dd, *J* = 10, 3.6 Hz, 1H), 3.14 (m, 1H), 3.02 (broad s, 1H), 1.90 (dt, *J* = 14.4, 10 Hz, 1H), 1.77 (dt, *J* = 14.4, 3.6 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 144.56, 129.26, 128.47, 128.45, 128.44, 127.55, 126.32, 125.66, 118.61, 115.17, 68.78, 50.78, 47.08, 24.82. MS (70 eV) *m/z* : 290.25 [M^+].

7.12.5 (*syn*)-1-phenyl-3-(phenylamino)butan-1-ol (10a) [8]

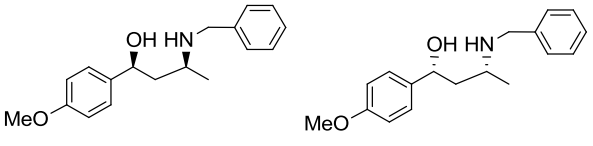



Yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.83 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.09-4.01 (m, 1H), 3.76 (s, 3H), 1.83 (dt, *J* = 14.8, 10.4 Hz, 1H), 1.69 (dt, *J* = 14.8, 3.2 Hz, 1H), 1.17 (d, *J* = 6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 158.93, 136.76, 126.89, 113.77, 74.73, 68.64, 55.25, 46.89, 24.76, 23.96. MS (70 eV) *m/z* : 197.11 [M^+].



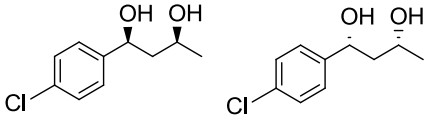
7.12.6 (*syn*)-3-(butylamino)-1-(4-methoxyphenyl)butan-1-ol (10b)

Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δδ 7.28 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.93 (dd, *J* = 11.2, 2 Hz, 1H), 3.04 (m, 1H), 3.81 (s, 3H), 2.84 (m, 1H), 2.57 (m, 1H), 1.71 (dt, *J* = 14.4, 2 Hz, 1H), 1.57-1.48 (m, 3H), 1.43-1.38 (m, 2H), 1.17 (d, *J* = 6.4Hz, 3H), 0.87 (t, *J* = 6Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 158.93, 136.76, 126.89, 113.77, 74.73, 60.64, 55.25, 46.89, 44.40, 30.59, 24.76, 20.74, 14.01. MS (70 eV) *m/z* : 252.19 [M^+].



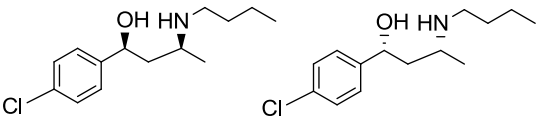
7.12.7 (*syn*)-(benzylamino)-1-(4-methoxyphenyl)butan-1-ol (10c)

Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.81 (dd, *J* = 11.2, 2 Hz, 1H), 3.71 (s, 3H), 3.11 (m, 5H), 1.62 (dd, *J* = 15.2, 10.8 Hz, 1H), 1.36 (dt, *J* = 15.2, 2.4 Hz,1H), 1.16 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 157.78, 136.15, 135.03, 130.22, 129.25, 128.58, 126.78, 113.75, 75.74, 57.04, 55.23, 54.56, 40.87, 19.24. MS (70 eV) *m/z*: 286.16 [M^+].



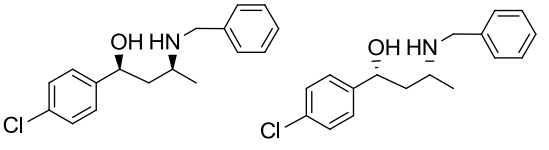
7.12.8 (*syn*)-1-(4-chlorophenyl)butane-1,3-diol (11a) [9]

Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 4.81 (dd, *J* = 10, 3.2 Hz, 1H), 4.07-3.97 (m, 1H), 3.53 (broad s, 2H), 1.74 (dt, *J* = 14.4, 10 Hz, 1H), 1.64 (dt, *J* = 14.4, 3.2 Hz, 1H), 1.14 (d, *J* = 6 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 143.06, 132.91, 128.44, 127.04, 74.19, 68.55, 46.82, 23.97. MS (70 eV) *m/z* : 201.06 [M^+].



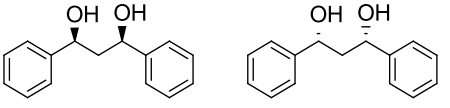
7.12.9 (*syn*)-3-(butylamino)-1-(4-chlorophenyl)butan-1-ol (11b)

Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 4.80 (dd, *J* = 10, 3.2 Hz, 1H), 3.10 (m, 1H), 2.84 (m, 1H), 2.57 (m, 1H), 1.78 (dt, *J* = 14.4, 2 Hz, 1H), 1.52 (m, 3H), 1.45 (m, 2H), 1.17 (d, *J* = 6.4Hz, 3H), 0.88 (t, *J* = 6Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 140.12, 132.76, 128.89, 127.77, 74.73, 55.64, 50.25, 46.89, 30.59, 25.76, 19.74, 14.01MS (70 eV) *m/z* : 256.14 [M^+].



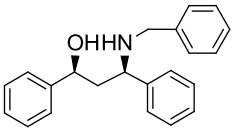
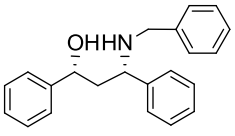
7.12.10 (*syn*)-3-(benzylamino)-1-(4-chlorophenyl)butan-1-ol (11c)

Yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 7.20 (d, *J* = 8.4 ,2H), 7.13 (d, *J* = 8.4, 2H), 4.84 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.68 (d, *J* = 10 Hz, 1H), 3.65 (d, *J* = 10 Hz, 1H), 3.11 (m, 1H), 1.59 (dt, *J* = 15.2, 10.8 Hz, 1H), 1.37 (dt, *J* = 15.2, 2.4 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 139.74, 138.40, 133.39, 131.58, 128.80, 127.89, 127.46, 116.78, 63.40, 55.24, 46.09, 27.39, 20.58. MS (70 eV) *m/z* : 290.12 [M^+].



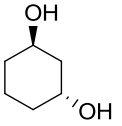
7.12.11 (*syn*)-1,3-diphenylpropane-1,3-diol (12a) [10]

Yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 – 7.24 (m, 5H), 7.21 – 7.16 (m, 5H), 4.92 (dd, *J* = 10, 2.4 Hz, 2H), 3.19 (broad, 1H), 2.13 (dt, *J* = 14.8, 10.4 Hz, 1H), 1.88 (dt, *J* = 14.8, 2.4 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 148.55, 128.50, 127.67, 125.75, 83.37, 51.49. MS (70 eV) *m/z* : 229.11 [M^+].

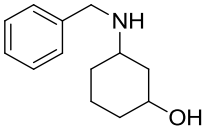
7.12.12 (*syn*)-3-(benzylamino)-1,3-diphenylpropan-1-ol (12c) [11]

Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 12H), 5.00 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.69 (m, 2H), 2.21 (dt, *J* = 14.8, 9.6 Hz,1H), 1.96 (dt, *J* = 14.8, 2.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 144.19, 142.74, 138.70, 128.84, 128.57, 128.43, 128.16, 127.61, 127.37, 126.55, 125.67, 125.60, 75.12, 60.81, 50.78, 47.89.. MS (70 eV) *m/z* : 318.18 [M^+].



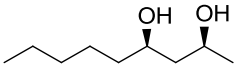
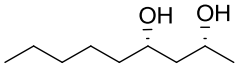
7.12.13 (*trans*)-cyclohexane-1,3-diol (17a) [12]

Yield 60%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.01-3.93 (m, 1H), 3.79 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.8-1.74 (m, 4H), 1.57 (m, 1H), 1.43 (m, 1H).^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 68.68, 34.03, 29.54, 22.65. MS (70 eV) *m/z* : 117.08 [M^+].



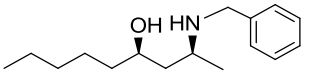
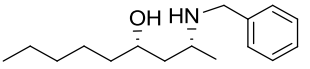
7.12.14 3-(benzylamino)cyclohexan-1-ol (17c, *synlanti* mixture) [13]

Yield 51%.^{1}H NMR (400 MHz, $CDCl_3$): δ7.74-7.09 (m, 5H), 4.12-4.01 (m, 0.3H), 3.83-3.69 (m, 0.7H), 3.81 (dd, *J* = 32.2, 12.8 Hz, 1.4H), 3.76 (dd, *J* = 12.8, 4.2 Hz, 0.6H), 2.96-2.87 (m, 0.3H), 2.86-2.77 (m, 0.7H), 1.91-1.79 (m, 1H), 1.82-1.67 (m, 2H), 1.69-1.46 (m, 4H), 1.47-1.33 (m, 2H), 1.34-1.16 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$): δ140.7, 140.0, 128.6, 128.2, 127.9, 127.1, 126.9, 126.8, 68.4, 66.8, 53.6, 51.6, 51.2, 39.9, 34.3, 33.7, 32.0, 31.6, 19.1. MS (70 eV) *m/z* : 206.15 [M^+].

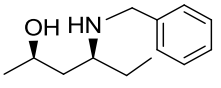
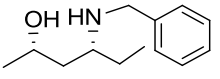
7.12.15 (*syn*)-nonane-2,4-diol (18a) [14]

Yield 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.96 (m, 1H), 3.79 (m, 1H), 1.54 (dt, *J* = 14.8, 2.4 Hz, 1H), 1.45 (dt, *J* = 14.8, 9.6 Hz, 1H), 1.30 (m, 10H), 1.14 (d, *J* = 6Hz, 3H); 0.83 (t, *J* = 7.2 Hz 7.2, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 73.20, 69.31, 44.54, 38.14, 31.73, 24.70, 24.10, 22.83, 14.22. MS (70 eV) *m/z* : 161.15 [M^+].

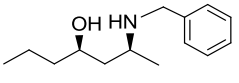
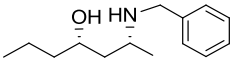
7.12.16 (*syn*)-2-(benzylamino)nonan-4-ol (18c)

Yield 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.33-7.23 (m, 5H), 3.82 (dd, *J* = 10.8, 2.4 Hz, 2H), 3.22 (m, 1H), 2.79 (m, 1H), 1.52 (dt, *J* = 14.8, 2.4 Hz, 1H), 1.47 (dt, *J* = 14.8, 9.6 Hz, 1H), 1.25 (m, 10H), 1.12 (d, *J* = 6Hz, 3H); 0.88 (t, *J* = 7.2 Hz 7.2, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 140.22, 128.50, 128.35, 127.90, 127.32, 69.82, 51.20, 49.62, 42.10, 37.72, 32.10, 25.07, 22.71, 21.87, 14.02. MS (70 eV) *m/z* : 250.22 [M^+].

7.12.17 (*syn*)-4-(benzylamino)hexan-2-ol (28c)

Yield 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.35-7.20 (m, 5H), 4.05 (m, 1H), 3.87 (dd, *J* = 10.6, 2.2 Hz, 2H), 2.61 (m, 1H), 1.52 (m, 4H), 1.10 (d, *J* = 6.8Hz, 3H); 0.89 (t, *J* = 7.2 Hz 7.2, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ140.87, 140.10, 128.40, 127.10, 126.92, 68.42, 52.20, 55,72, 41.69, 28.33, 23.44, 11.2. MS (70 eV) *m/z* : 208.17 [M^+].

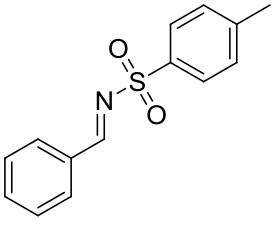
7.12.18 (*syn*)-2-(benzylamino)heptan-4-ol (29c)

Yield 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.31-7.19 (m, 5H), 3.90 (dd, *J* = 10.4, 2.4 Hz, 2H), 3.29 (m, 1H), 2.80 (m, 1H), 1.50 (dt, *J* = 14.8, 2.4 Hz, 1H), 1.40 (dt, *J* = 14.8, 9.6 Hz, 1H), 1.28 (m, 4H), 1.12 (d, *J* = 6Hz, 3H); 0.89 (t, *J* = 7.2 Hz 7.2, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ141.02, 128.32, 127.89, 127.13, 126.98, 69.49, 51.88, 49.56, 43.10, 39.80, 22.01, 18.88, 14.50. MS (70 eV) *m/z* : 222.19 [M^+].

7.13 General methodology for the synthesis of the tosylaldimines

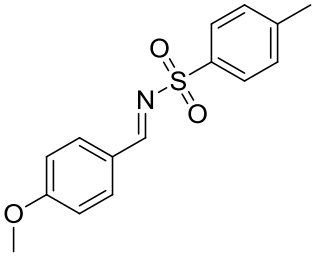
The amine (1.1 mmol), aldehyde (1 mmol), and montmorillonite K10 as catalyst and dehydrating agent (100 mg) were stirred in toluene (2.5 mL) overnight. The solution was filtered through a pad of celite, and the product was isolated by removing all the volatiles in vacuum, using a Kugelrohr apparatus, and used without further purification.

7.14 Characterization of tosylaldimines:



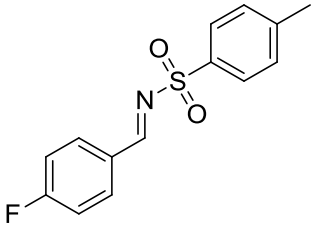
7.14.1. Synthesis of (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (30) [15]

Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ170.28, 144.69, 135.00, 132.31, 131.32, 129.83, 129.15, 128.06, 126.33, 21.66; MS (70 eV) *m/z* : 260.07 [M^+].



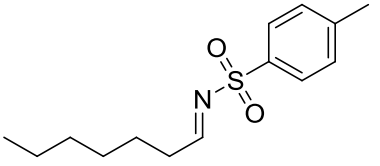
7.14.2 Synthesis of (*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (31) [16]

Yield 85%. ^{1}H NMR ($CDCl_3$, 400MHz) δ 9.06 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 169.53, 165.30, 144.32, 133.74, 129.74, 127.83, 126.35, 125.03, 114.59, 55.75, 21.61. MS (70 eV) *m/z* : 290.08 [M^+].



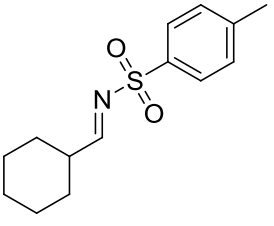
7.14.3 Synthesis of (*E*)-*N*-(4-fluorobenzylidene)-4-methylbenzensulfonamide (32) [17]

Yield 83%. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 9.12 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.8, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.31(d, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 168.95, 165.44, 144.86, 133.56, 129.98, 127.90, 126.49, 116.53, 21.57. MS (70 eV) *m/z* : 278.06 [M^+].



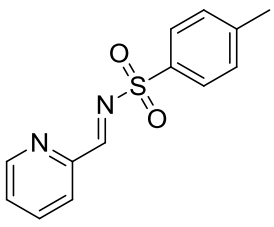
7.14.4 Synthesis of (*E*)-4-methyl-*N*-heptylidenebenzenesulfonamide (33) [18]

Yield 98%. ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.58 (t, *J* = 4.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 2.42 (s, 3H), 1.62-1.54 (m, 2H), 1.32-1.22 (m, 6H), 0.87-0.78 (m, 5H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 167.13, 143.26, 139.29, 129.56, 126.18, 31.58, 28.45, 26.58, 25.52, 22.37, 21.85, 13.99. MS (70 eV) *m/z* : 268.13 [M^+].



7.14.5 Synthesis of (E)-N-(cyclohexylmethylene)-4-methylbenzenesulfonamide (34) [19]

Yield 98%. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 8.51 (d, *J* = 4.4 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 2.45-2.43 (m, 1H), 2.38 (s, 3H), 2.01-1.87 (m, 4H), 1.79-1.54 (m, 4H), 1.35 (t, *J* = 10.8 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 163.47, 144.62, 134.77, 129.50, 127.91, 35.55, 28.74, 25.81, 25.00, 21.32. MS (70 eV) *m/z*: 266.12 [M^+].



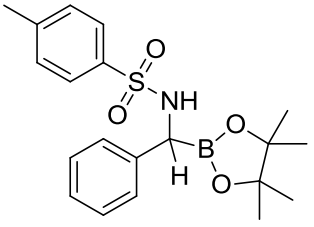
7.14.6 Synthesis of (*E*)-4-methyl-*N*-(pyridin-2-ylmethylene)benzenesulfonamide (35) [20]

Yield 64%. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 9.19 (s, 1H), 9.15 (d, *J* = 2 Hz, 1H), 8.92 (dd, *J* = 2, 4.8 Hz , 1H), 8.31 (dt, *J* = 2, 8.4 Hz , 1H), 8.06 (d, *J* = 8.4 Hz , 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz) δ 169.23, 161.36, 148.73, 144.30, 137.49, 130.08, 129.56, 128.80, 127.98, 124.85, 21.85. MS (70 eV) *m/z* : 261.07 [M^+].

7.15 Experimental procedure for the enantioselective base/phosphine catalyzed borylation of N-tosyl aldimines with bis(pinacolato)diboron

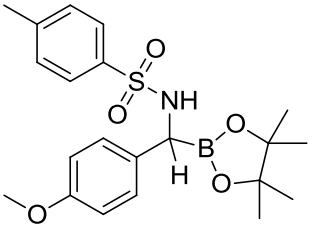
The reactions were carried out in a Carousel multireactor. The Cs_2CO_3 (12.2 mg, 0.0375 mmol), the chiral phosphine (0.02-0.04 mmol), and B_2pin_2 (76.2 mg, 0.3 mmol) were transferred into the reaction tubes of the reactor. The reaction vessels were purged with argon. THF (0.75 mL), THF solution of the substrate, (250 µL of 1M THF solution, 0.25 mmol), and MeOH (50 mL, 40 mg, 1.25 mmol) were added, and the reaction mixtures were stirred at 70 or 45 °C external temperature for 15 hours, or at room temperature for 24 hours. 200 µl of the reaction mixture was taken as analytical sample, it was diluted with 400 µL of $CDCl_3$, and analyzed by ^{1}H-NMR. The NMR sample was used to prepare the sample for the chiral HPLC analysis. The volatiles were evaporated from the NMR sample, the residue was dissolved in the eluent of the chiral HPLC-TOF analysis, and the sample was analyzed immediately to determinate the enantioselectivity.

7.16 Characterization of α–amino boronate esters:



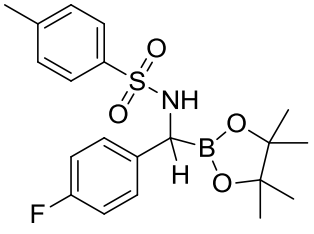
7.16.1 Synthesis of 4-methyl-*N*-((phenyl)(pinacolatoboryl)methyl) benzenesulfonamide (30a)

Yield 78 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.18-7.09 (m, 5H), 4.95 (d, *J* = 6.4 Hz, 1H), 4.03 (d, *J* = 6.4 Hz, 1H), 2.34 (s, 3H), 1.18 (s, 6H), 1.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.40, 136.83, 136.41, 129.65, 128.74, 127.98, 127.09, 113.33, 83.57, 55.17, 24.93, 24.04, 21.65. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 31.81. MS (70 eV) *m/z* : 388.17 [M^+].



7.16.2. Synthesis of 4-methyl-*N*-((4-methoxyphenyl)(pinacolatoboryl)methyl) benzenesulfonamide (31a)

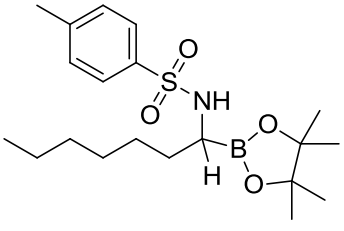
Yield 62%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 4.85 (d, *J* = 6 Hz, 1H), 3.96 (d, *J* = 6 Hz, 1H), 3.72 (s, 3H), 2.35 (s, 3H), 1.18 (s, 6H), 1.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 159.11, 143.42, 136.84, 129.72, 129.48, 127.39, 126.86, 113.23, 84.66, 64.74, 55.30, 24.92, 24.41, 21.47. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.51. MS (70 eV) *m/z* : 435.17 [$M+NH_4^+$].



7.16.3 Synthesis of 4-methyl-*N*-((4-fluorophenyl)(pinacolatoboryl)methyl) benzenesulfonamide (32a)

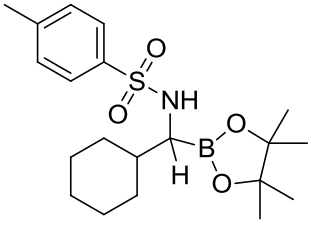
Yield 79 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 8.8, 8.4 Hz, 2H), 4.92 (d, *J* = 6.4 Hz, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 2.36 (s, 3H), 1.18 (s, 6H), 1.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz)

δ163.85, 143.91, 137.09, 130.05, 129.96, 129.88, 127.43, 115.91, 115.69, 84.01, 56.87, 25.32, 24.31, 21.84. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 32.71. MS (70 eV) *m/z* : 423.15 [M+NH_4^+].



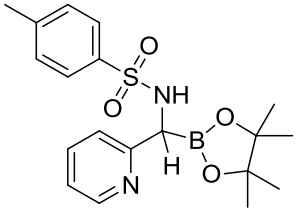
7.16.4 Synthesis of 4-methyl-*N*-(1-(pinacolatoboryl)heptyl)benzenesulfonamide (33a)

Yield 82 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 10 Hz, 2H), 7.72 (d, *J* = 10 Hz, 2H), 3.43 (d, *J* = 5.6 Hz, 1H), 2.78 (t, *J* = 5.6 Hz, 1H), 2.35 (s, 3H), 1.88-1.83 (m, 2H), 1.25-1.06 (m, 20H), 0.82 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 129.55, 127.13, 83.69, 49.08, 31.67, 29.47, 28.92, 27.52, 24.97, 24.52, 22.56, 21.45, 14.04. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.79. MS (70 eV) *m/z* : 396.23 [M^+].



7.16.5 Synthesis of 4-methyl-*N*-((cyclohexyl)(pinacolatoboryl)methyl) benzenesulfonamide (34a)

Yield 20 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 1H), 3.4 (d, *J* = 6.4 Hz, 1H), 2.38 (s, 3H), 1.73-1.57 (m, 6H), 1.21 (s, 6H), 1.19 (s, 6H), 1.16-1.02 (m, 3H), 0.92-0.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.29, 137.09, 129.69, 126.91, 83.35, 60.58, 37.68, 30.49, 26.21, 25.60, 24.97, 24.79, 21.47. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 33.83. MS (70 eV) *m/z* : 394.22 [M^+].



7.16.6 Synthesis of 4-methyl-*N*-((pyridine-2-yl)(pinacolatoboryl)methyl) benzenesulfonamide (35a)

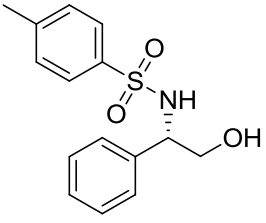
Yield 68%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, *J* = 3.2 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.60 (dd, *J* = 7.6, 10.4 Hz, 1H), 7.49 (d, *J* = 10.4 Hz, 1H), 7.41 (dd, *J* = 3.2, 7.6 Hz 1H), 7.24 (d, *J* =

8.4 Hz, H), 5.54 (d, *J* = 6.4 Hz, 1H), 4.08 (d, *J* = 6.4 Hz, 1H), 2.37 (s, 3H), 1.18 (s, 6H), 1.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.67, 143.58, 136.79, 135.94, 131.86, 129.93, 128.66, 127.20, 123.57, 84.21, 59.53, 44.60, 24.81, 24.41, 21.38. ^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 31.40. MS (70 eV) *m/z* : 389.17 [M^+].

7.17 Borylation/Homologation/Oxidation procedure to obtain β–amino alcohols

The reactions were carried out in a Carousel multireactor. The Cs_2CO_3 (12.2 mg, 0.0375 mmol), the chiral phosphine (0.02-0.04 mmol), and B_2pin_2 (76.2 mg, 0.3 mmol) were transferred into the reaction tubes of the reactor. The reactions vessels were purged with argon. THF (0.75 mL), THF solution of the substrate (250 µL of 1M THF solution, 0.25 mmol), and MeOH (50 mL, 40 mg, 1.25 mmol) were added, and the reaction mixtures were stirred at 45 °C external temperature for 15 hours. Bromochloromethane (30 µL, 0.3 mmol) was added, and the solution was cooled to -78 °C. To this solution n-BuLi (188 µL of 1.6 M solution, 0.3 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 10 min. It was allowed to warm to room temperature, and stirred for 8.5 hours. Aqueous hydrogen peroxide (200 µL, 30%), and NaOH solution (0.4 mL, 5%) were added to the reaction mixture. The reaction mixture was stirred for 2.5 hours, and then it was quenched with saturated sodium thiosulfate solution. The reaction mixture was extracted with ethyl acetate for three times. The combined organic phase was washed with brine, and dried over Na_2SO_4. The Na_2SO_4 was filtered off, and all the volatiles were removed in vacuum. The crude product was purified by a flash column chromatography and analyzed be ^{1}H-NMR and chiral HPLC-TOF to characterize.

7.18 Characterization of β–amino alcohol:



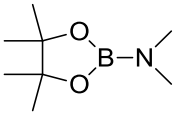
7.18.1 Synthesis of (*S*)-*N*-(2-hydroxy-1-phenylethyl)-4-methylbenzenesulfonamide (30b) [21]

Yield 82 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.31-7.23 (m, 2H), 7.08-7.02 (m, 3H), 4.80 (d, *J* = 7.6 Hz, 1H), 4.21 (dd, *J* = 7.6, 14.4 Hz, 1H), 3.75 (d, *J* = 10.8 Hz ,1H), 3.66 (d, *J* = 14.4 Hz ,1H), 2.36 (s, 3H), 1.97 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 141.90, 140.02, 138.10, 128.69, 128.22, 127.35, 125.99, 125.43, 60.99, 57.35, 21.31. MS (70 eV) *m/z*: 330.05 [M+K$^+$].

7.19 Methodology for synthesis of the amino-pinacolborane reagents [22]

BCl_3 (5mL, 1M in toluene, 5 mmol) was dropwise added to a solution of dimethylamine (15mL, 2M in THF, 30 mmol) or diethylamine (15mL, 2M in THF, 30 mmol) at -78ºC, under argon. The solution was stirred during 5 h at low temperature and 16 h at room temperature. After that period, the solid tris(dimethylamino)borane or tris(diethylamino)borane was filtrated and dissolved in THF (30mL) with pinacol (0.66 g, 5.5 mmol). The mixture was heated to reflux for 24 hours, and the reaction product was checked by NMR. The desired products were isolated distillation with Kugelrohr apparatus (T= 60ºC) as a white solid.

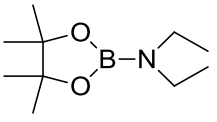
7.20 Characterization of amino-pinacolborane reagents:



7.20.1. Synthesis of dimethylamino-pinacolborane reagent (36a)

Yield 90%.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 6 H), 1.19 (s,

12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 83.52, 34.77, 24.82.^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 24.44. MS (70 eV) *m/z* : 172.15 [M^+].



7.20.2. Synthesis of diethylamino-pinacolborane reagent (36b)

Yield 85%.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (q, *J* = 6.4 Hz, 4 H), 1.42 (t, *J* = 6.4 Hz, 6H), 1.17 (s, 12H).$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 82.77, 41.87, 24.85, 13.55.^{11}B NMR ($CDCl_3$, 128.3 MHz) δ 24.85. MS (70 eV) *m/z* : 200.18 [M^+].

7.21 General procedure of the amination of α,β–unsaturated compounds with [$RO^- \rightarrow B(OR)_2$-$N(R')_2$]

The phosphine, (tricyclohexylphosphine 5.6 mg, 0.02 mmol), base (NaO*t*Bu, 0.03 mmol) and dimethylamino-pinacolborane (275 µL of 1M MeOH solution 0.275mmol) were transferred into an oven-dried Schlenk tube under nitrogen with methanol (2 mL). The substrate (0.25 mmol) was then added and the reaction mixture was stirred at 70 °C external temperature. After 17 hours 200 µl of the reaction mixture was taken as an analytical sample to analyzed the conversion by ^{1}H NMR and/or GC analysis. The crude product was purified by flash column chromatography.

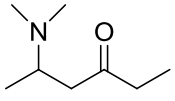
7.22 Experimental procedure of the C=O reduction of the β–dimethylamino ketones to obtain the final γ-aminoalcohols.

To a stirred solution of the β-dimethylamino ketone (0.5 mmol) in dry THF or MeOH (2.5 ml), at the temperature and solvent specified in **7.9.1.-7.9.3.**, the reducing agent (1.5 mmol) was slowly added under argon. After the reaction time specified in **7.9.1.-7.9.3.**, the solution was partitioned between dichloromethane and saturated NaCl (aq.). The combined organic phases were dried, and the solution was concentrated in vacuum. The obtained cloudy oil was analyzed

directly by ^{1}H-NMR to determine conversion and diastereoselectivities. The crude products were purified by column chromatography on silica gel (CH_3Cl/CH_2Cl_2) to give the major diastereomers.

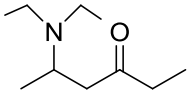
7.23 Characterization of β–amino ketones, β-enamino esters and γ-dimethylamino alcohols:

7.23.1 Synthesis of 5-dimethylamino-hexan-3-one (40a) [23]

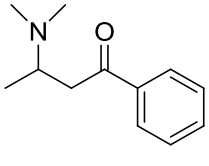


Yield 88 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14-3.06 (m, 1H), 2.60 (dd, *J* = 15.2, 5.2 Hz, 1H), 2.37 (q, *J* = 7.2 Hz, 2H), 2.28 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.20 (s, 6H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 210.69, 55.31, 45.71, 40.31, 36.39, 14.23, 7.68. MS (70 eV) *m/z* : 144.14 [M^+].

7.23.2 Synthesis of 5-(diethylamino)hexan-3-one (40b)



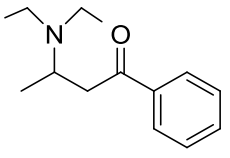
Yield 27 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14-3.06 (m, 1H), 2.85 (dd, *J* = 15.2, 5.2 Hz, 1H), 2.71 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.60 (q, *J* = 7.2 Hz, 2H), 2.51 (q, *J* = 7.6 Hz, 2H), 2.15 (s, 6H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.44, 54.78, 43.37, 35.98, 28.26, 25.85, 18.45. MS (70 eV) *m/z* : 172.17 [M^+].



7.23.3 Synthesis of 3-(dimethylamino)-1-phenylbutan-1-one (41a) [24]

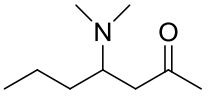
Yield 84 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz ,1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.6 Hz, 2H), 3.34-3.29 (m, 1H), 3.24 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.85 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.27 (s, 6H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.47, 145.22, 133.35,132.98, 128.69, 128.09, 56.23,41.68,40.44, 14.96. MS (70 eV) *m/z* : 192.14 [M^+].

7.23.4 Synthesis of 5-(diethylamino)hexan-3-one (41b) [25]

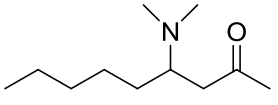


Yield 32 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz ,1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.44 (dd, *J* = 8.4, 7.6 Hz, 2H), 3.45-3.30 (m, 1H), 3.27 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.83 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 6H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.44, 55.60, 49.98, 41.70, 15.75, 13.76. MS (70 eV) *m/z* : 220.17 [M^+].

7.23.5 Synthesis of 4-(dimethylamino)heptan-2-one (42)



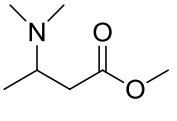
Yield 68 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.01-2.96 (m, 1H), 2.56 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.26 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.17 (s, 6H), 2.09 (s, 3H), 1.48-1.39 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 208.72, 60.30, 42.75, 40.10, 29.98, 25.86, 22.34, 14.10. MS (70 eV) *m/z* : 158.15 [M^+].



7.23.6 Synthesis of 4-(dimethylamino)nonan-2-one (43)

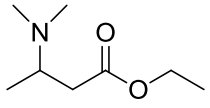
Yield 65 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.04-2.97 (m, 1H), 2.61 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.31 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.19 (s, 6H), 2.14 (s, 3H), 1.49-1.41 (m, 2H), 1.32-1.18 (m, 6H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 208.98, 60.44, 43.95, 40.24, 30.19, 27.78, 26.83, 22.81, 14.37. MS (70 eV) *m/z* : 186.19 [M^+].

7.23.7 Synthesis of methyl 3-(dimethylamino)butanoate (46) [26]



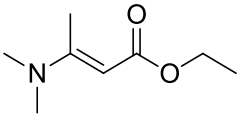
Yield 37 %. ^{1}H NMR ($CDCl_3$, 400 52MHz) δ 3.54-3.52 (m, 1H), 3.21 (s, 3H), 2.49 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.35 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.10 (s, 6H), 1.14 (d, *J* = 6.4 Hz, 3H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.73, 58.42, 54.72, 50.70, 45.32, 32.52. MS (70 eV) *m/z* : 146.12 [M^+].

7.23.8Synthesisofethyl 3-(dimethylamino)butanoate (47) [27]



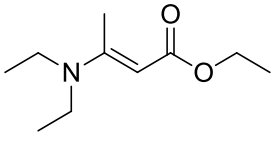
Yield 58 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (q, *J* = 7.2 Hz, 2H), 3.67-3.62 (m, 1H), 2.50 (dd, *J* = 19.2, 5.2 Hz, 1H), 2.28 (dd, *J* = 19.2, 8.4 Hz, 1H), 2.14 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.68, 60.10, 51.03, 41.62, 39.93, 18.07, 14.37. MS (70 eV) *m/z* : 160.13 [M^+].

7.23.9 Synthesis of (*E*)-ethyl 3-(dimethylamino)but-2-enoate (53a, *E:Z* mixture 85:15) [28]

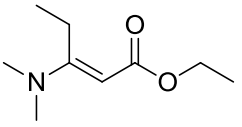


Yield 68 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.37 (s, 0.15H), 5.29 (s, 0.85H) (the irradiation of the vinylic protonat 5.29 ppm resulted in no enhancement of the allylic proton signal), 4.29 (q, *J* = 7.2 Hz, 0.3H), 4.21 (q, *J* = 7.2 Hz, 1.7H), 3.81 (s, 0.45H), 3.73 (s, 2.55H), 3.54 (s, 0.45H), 3.46 (s, 2.55H), 2.34 (s, 0.45H), 2.26 (s, 2.55H), 1.37 (t, *J* = 7.2 Hz, 0.45H), 1.37 (t, *J* = 7.2 Hz, 2.55H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.11, 165.74, 81.86, 61.38, 50.12, 17.09, 14.24. MS (70 eV) *m/z* : 158.12 [M^+].

7.23.10 Synthesis of (*E*)-ethyl 3-(diethylamino)but-2-enoate (53b)

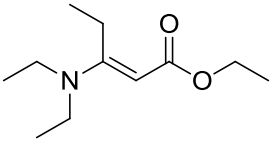


Yield 62 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59 (s, 1H) (the irradiation of the vinylic protonat 4.59 ppm resulted in no enhancement of the allylic proton signal), 4.10 (q, *J* = 7.2 Hz, 2H), 3.29 (q, *J* = 7.2 Hz, 4H), 2.46 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.54, 159.87, 82.75, 58.18, 43.93, 14.97, 14.75, 12.84. MS (70 eV) *m/z* : 186.15[M^+].



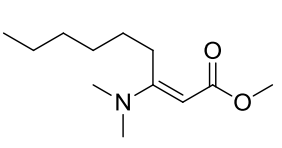
7.23.11 Synthesis of (*E*)-ethyl 3-(dimethylamino)pent-2-enoate (54a, *E:Z* mixture 88:12)

Yield 74 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.22 (s, 0.12H), 5.03 (s, 0.88H), 4.20 (q, *J* = 7.2 Hz, 0.24H), 4.12 (q, *J* = 7.2 Hz , 1.76H), 3.65 (s, 0.36H), 3.55 (s, 2.64H), 3.45 (s, 0.36H), 3.34 (s, 2.64H), 3.05 (q, *J* = 7.6 Hz, 0.24H), 2.91 (q, *J* = 7.6 Hz, 1.76H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.09, 165.72, 81.39, 61.84, 53.94, 52.59, 36.06, 14.22, 7.66. MS (70 eV) *m/z* : 172.13 [M^+].



7.23.12 Synthesis of (*E*)-ethyl 3-(diethylamino)pent-2-enoate (54b)

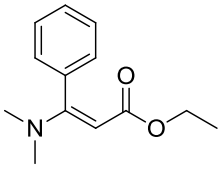
Yield 60 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.45 (s, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.21 (q, *J* = 7.2 Hz , 4H), 2.89-2.81 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.91 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.19, 159.31, 82.36, 57.52, 42.94, 20.96, 15.86, 15.28, 12.71.MS (70 eV) *m/z* : 200.17 [M^+].



7.23.13 Synthesis of (*E*)-methyl 3-(dimethylamino)non-2-enoate (55)

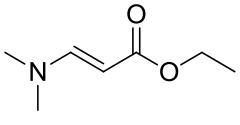
Yield 63 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.97 (s, 1H) (the irradiation of the vinylic protonat 4.97 ppm resulted in no enhancement of the allylic proton signal), 3.72 (s, 3H), 3.53 (s, 3H), 3.44 (s, 3H), 2.02 (t, *J* = 7.2 Hz, 2H), 1.63-1.52 (m, 2H), 1.33-1.22 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.66, 165.33, 88.96, 51.99, 49.02, 43.32, 31.17, 28.52, 24.10, 22.44, 14.37. MS (70 eV) *m/z* : 214.18 [M^+].

7.23.14 Synthesis of (*E*)-ethyl 3-(dimethylamino)-3-phenylacrylate (56)



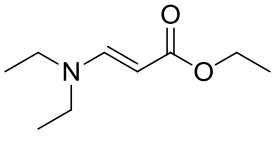
Yield 85 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.32 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 5.43 (s, 1H) (the irradiation of the vinylic protonat 5.29 ppm resulted in enhancement of the methyl proton signal at 3.39 ppm), 3.86 (q, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 3.27 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.98, 164.29, 134.05, 128.99, 128.37, 127.62, 126.35, 85.99, 61.80, 45.96, 14.07. MS (70 eV) *m/z* : 220.13 [M^+].

7.23.15 Synthesis of (*E*)-ethyl 3-(dimethylamino)acrylate (57a) [29]



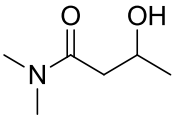
Yield 93 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (d, *J* = 13.2 Hz, 2H), 4.17 (d, *J* = 13.2 Hz ,1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.43 (s, 3H), 3.07 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.52, 152.48, 84.02, 58.43, 38.38, 14.43. MS (70 eV) *m/z* : 144.10 [M^+].

7.23.16 Synthesis of (*E*)-ethyl 3-(diethylamino)acrylate (57b)



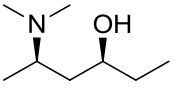
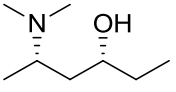
Yield 90 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J* = 13.2 Hz, 2H), 4.51 (d, *J* = 13.2 Hz ,1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.14 (q, *J* = 7.2 Hz, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.10, 151.02, 83.64, 62.35, 58.80, 14.97, 13.94. MS (70 eV) *m/z* : 172.13 [M^+].

7.23.17 Synthesis of 3-hydroxy-N,N-dimethylbutanamide (59) [30]



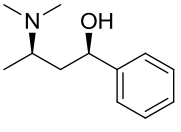
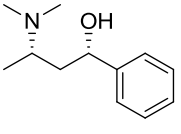
Yield 92 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.18-4.12 (m, 1H), 2.95 (s, 3H), 2.91 (s, 3H), 2.46 (dd, *J* = 16.4, 2 Hz, 1H), 2.29 (dd, *J* = 16.4, 9.6 Hz, 1H), 1.18 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.44, 64.51, 41.05, 37.33, 35.37, 22.14. MS (70 eV) *m/z* : 132.10 [M^+].

7.23.18 Synthesis of *syn*-5-(dimethylamino)hexan-3-ol (60)

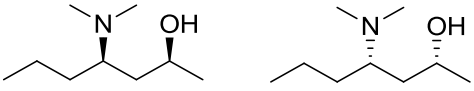



Yield 92-85 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.71-3.61 (m, 1H), 2.89-2.81 (m, 1H), 2.17 (s, 6H), 1.44-1.28 (m, 4H), 1.23 (dt, *J* = 2.4, 14.4 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 74.73, 60.43, 40.88, 39.36, 38.26, 30.82, 11.38, 9.82. MS (70 eV) *m/z* : 146.15 [M^+].

7.23.19 Synthesis of *syn*-3-(dimethylamino)-1-phenylbutan-1-ol (61) [31]

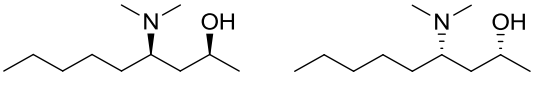



Yield 88 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.24 (m, 5H), 4.85 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.05-3.01 (m, 1H), 2.23 (s, 6H), 1.71 (dt, *J* = 14.8, 10.8 Hz, 1H), 1.43 (dt, *J* = 14.8, 2.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 146.63, 131.96, 131.27, 128.80, 72.14, 61.82, 40.19, 38.99, 17.96. MS (70 eV) *m/z* : 194.15 [M^+].



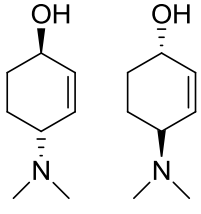
7.23.20 Synthesis of *syn*-4-(dimethylamino)heptan-2-ol (62)

Yield 62 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89-3.82 (m, 1H), 2.58-2.52 (m, 1H), 2.20 (s, 6H), 1.41-1.11 (m, 6H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 69.68, 65.41, 40.38, 39.79, 37.45, 28.09, 23.84, 20.63, 14.51. MS (70 eV) *m/z* : 160.17 [M^+].



7.23.21 Synthesis of *syn*-4-(dimethylamino)nona-2-ol (63)

Yield 58 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89-3.79 (m, 1H), 2.57-2.50 (m, 1H), 2.23 (s, 6H), 1.53-1.39 (m, 6H), 1.38-1.29 (m, 4H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 69.74, 65.77, 39.50, 37.54, 31.97, 28.82, 27.21, 25.90, 22.41, 13.96. MS (70 eV) *m/z* : 188.20 [M^+].



7.23.22Synthesisof*trans*-(dimethylamino)cyclohex-2-enol (65) [32]

Yield 37 %. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (dd, *J* = 10.4, 2.8 Hz, 1H), 5.95 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.57 (td, *J* = 9.2, 2.8 Hz, 1H), 2.95 (dt, *J* = 8.8, 2.0 Hz, 1H), 2.22 (s, 6H), 2.21-2.15 (m, 2H), 2.10-2.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 130.17, 122.36, 68.13, 67.22, 40.94, 29.07, 24.87. MS (70 eV) *m/z* : 142.12 [M^+].

7.24 References

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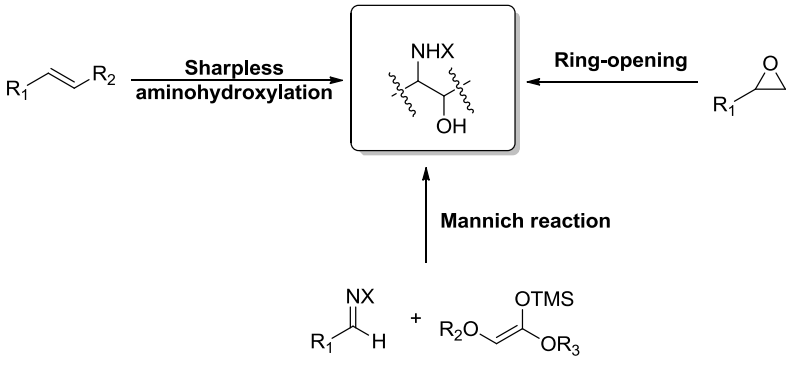
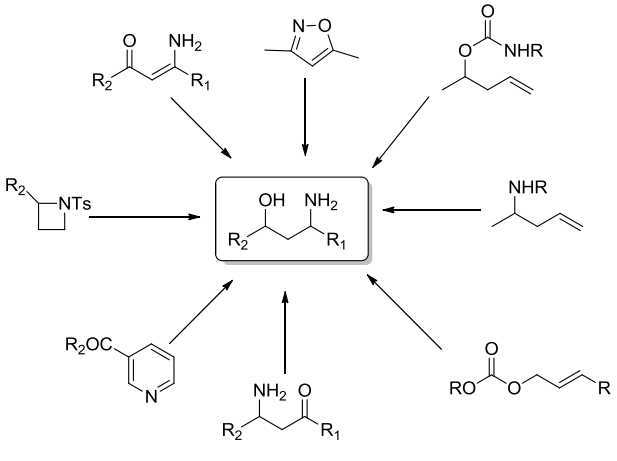
Chapter 8: Summary/Resum

Amino alcohols are important building blocks extensively employed for the synthesis of natural products [1], pharmaceuticals [2], and for the production of chiral auxiliaries or catalysts, to be used in asymmetric synthesis. [3] In the last decade many protocols have been developed for the selective asymmetric synthesis of these compounds. The β–amino alcohols can be synthesized through ring-opening of epoxides, [4] using the Sharpless asymmetric aminohydroxylation [5] or stereoselective Manninch-type reaction (Scheme 8.1). [6]



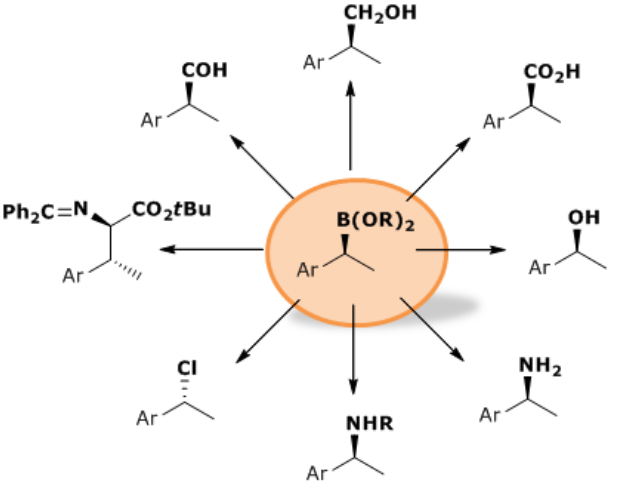
Scheme 8.1 Three different methods to obtain β–amino alcohols.

The most relevant methods to synthesize γ–amino alcohols are reductions with metal hydride or catalytic hydrogenation of enaminones, [7] isoxazoles or isoxazolines, [8] β-amino carbonyl compounds, [9] ketopyridines, [10] ring opening of azetidines [11] or allylic reactions (Scheme 8.2). [12]



Scheme 8.2 Common methods to obtain γ–amino alcohols.

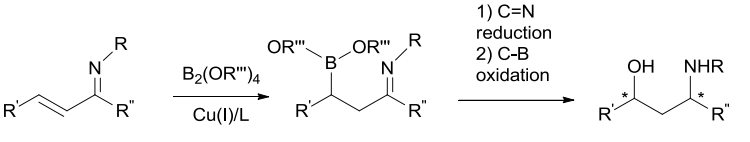
Organoboranes can be utilized as interesting intermediates in organic chemistry. [13] The C-B bond formation can be transformed into C-O, C-N, C-C and C-X bond having the configuration retained in the functionalization process (Scheme 8.3).



Scheme 8.3 Examples of the C-B bond transformations.

Taking into consideration the advantages of organoboronic esters in organic synthesis, four new one-pot routes to synthesize β– or γ–amino alcohols have been developed in this thesis.

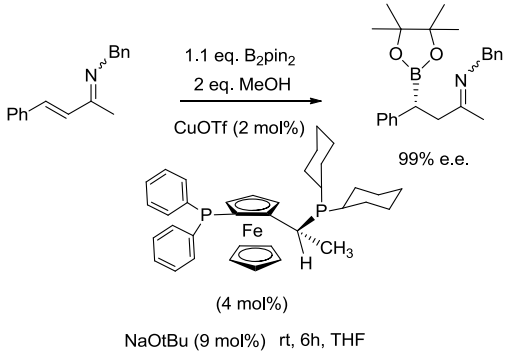
The first one-pot route was based on the catalytic β–boration of α,β–unsaturated imines followed by reduction of the corresponding imine and oxidation of C-B bond to obtain the desired γ–amino alcohol structure (Scheme 8.4).



Scheme 8.4 One-pot catalytic β–boration of α,β–unsaturated imines followed by reduction/oxidation.

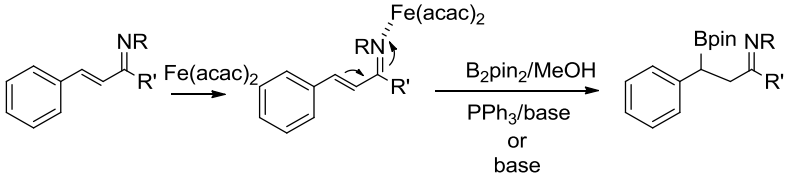
A range of aryl α,β–unsaturated imines have been synthesized to become substrates of the copper catalyzed β–boration reaction. High conversions were

independently achived despite the nature of the imino substituent. When chiral phosphorus ligands were used to modify the copper (I) salts, high enantioselectivities were induced (up to 99 *e.e.*%) (Scheme 8.5).



Scheme 8.5 Copper(I) salts modified with Josiphos-type ligands induced 99% of enantioselectivity in the β–boration of 1-phenyl-N-((*E*)-4-phenylbut-3-en-2-ylidene)methanamine.

Not only copper was the metal used as catalyst, we were interested in the iron β–boration of α,β–unsaturated imines. In this case, the iron was not responsible to activate the diboron reagent and it seems that the role of iron was the activation of the substrates by the Lewis acidic character (Scheme 8.6).



Scheme 8.6 The role of iron in the β–boration of α,β–unsaturated imines

After the study of the catalyzed β–boration of α,β–unsaturated imines, we were interested in the 1,3-diastereocontrolled reduction of the β–boryl imines. Six different reducing agent were applied and finally in collaboration with Prof. A. Whiting, we obtained a total control to the *syn* or *anti* diastereoisomer γ–amino alcohol formation (Figure 8.1).

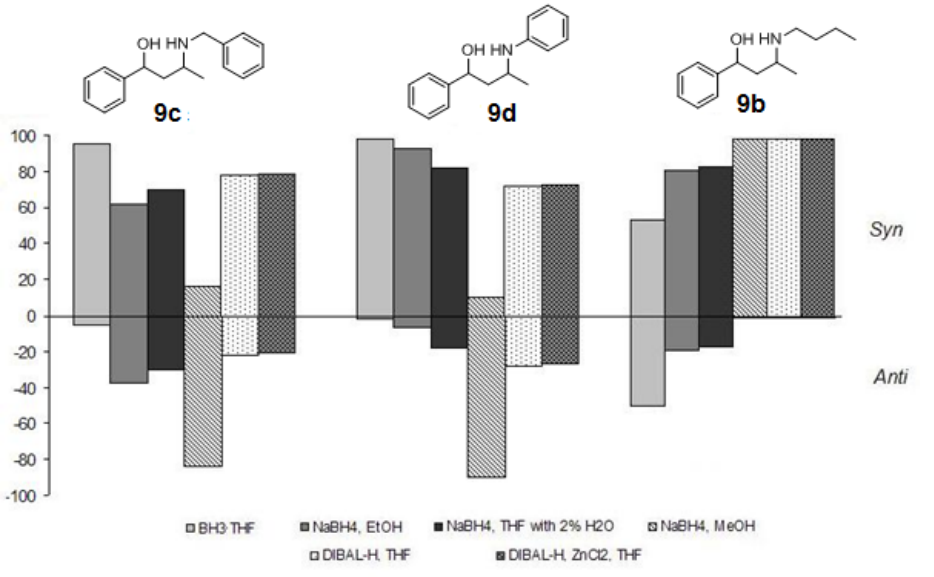
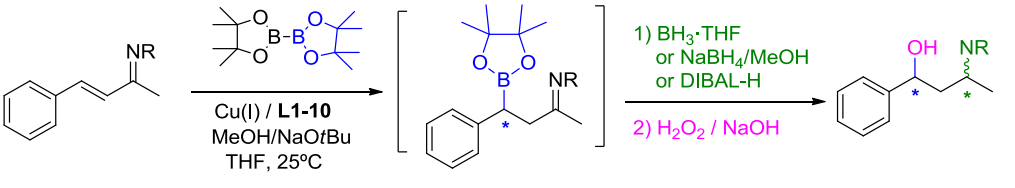


Figure 8.1 1,3-Diastereocontrol in the reduction/oxidation process of β–boryl imines towards the synthesis of γ–amino alcohols.

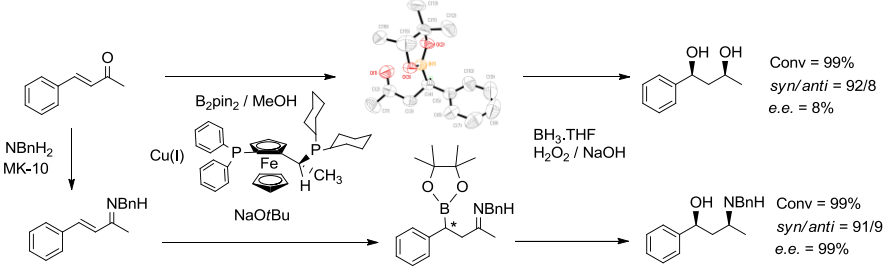
Once the diastereoselective reduction had been optimized, we developed the stereoselective one-pot β–boration/reduction/oxidation process. The enantioselectivities induced in the copper catalysed β–boration are remained in the reduction/oxidation process and, consequently, we were able to obtain enantio- and diastereoenriched γ–amino alcohols (Scheme 8.7).



Scheme 8.7 Stereoselective one-pot β–boration/reduction/oxidation of α,β–unsaturated imines to synthesize chiral enantioenriched γ–amino alcohols.

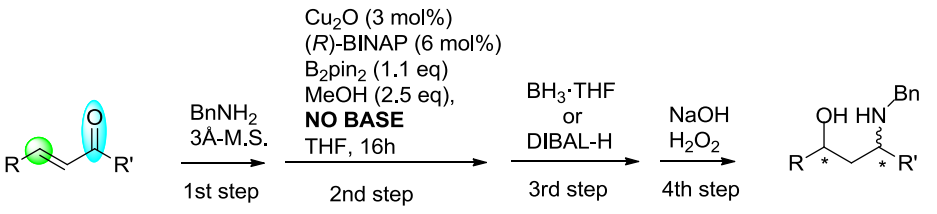
A comparative study of the one-pot approach to a range of α,β–unsaturated ketones were carried out. Important differences were found between β–boryl

imines and ketones in the boron signals. The shift to higher field of the β–boryl imines is diagnostic of a possible intramolecular interaction between N and B that can affect the diastereoselective control of the reduction process. Fourteen enantioenriched 1,3-difunctionalized molecules were synthesized using the one-pot reaction sequence β–boration/reduction/oxidation of activated ketones and imines (Scheme 8.8).



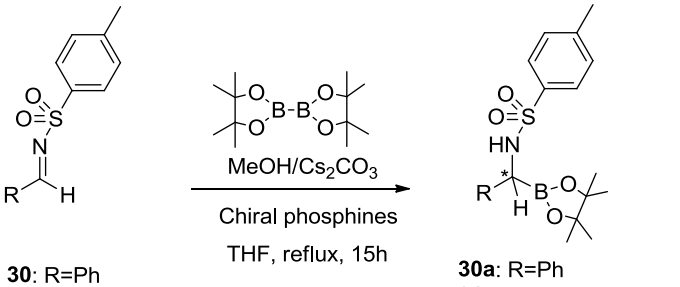
Scheme 8.8 One-pot β–boration/reduction/oxidation of activated ketones and imines.

The second novel one-pot 4-step sequence was developed in collaboration with Prof. A. Whiting (Durham University). We were able to prepare in *situ* the imine followed by the β–boration/reduction/oxidation process. This methodology allowed us to focus the 4-step one-pot route on aliphatic α,β–unsaturated ketones to obtain the corresponding γ–amino alcohols. In addition, we discovered a new base-free asymmetric copper system (Cu_2O) modified with cheap chiral phosphorus ligands to catalyze the β–boration step. Consequently, we synthesized nine γ–amino alcohols using a one-pot four step sequence and demonstrate that this new methodology can be a general novel route to synthesize enriched γ–amino alcohols (Scheme 8.9).



Scheme 8.9 Imine formation/β-boration using Cu_2O and (*R*)-BINAP/reduction/oxidation is the new 4-step one-pot procedure to synthesize allylic enantioenriched γ-amino alcohols.

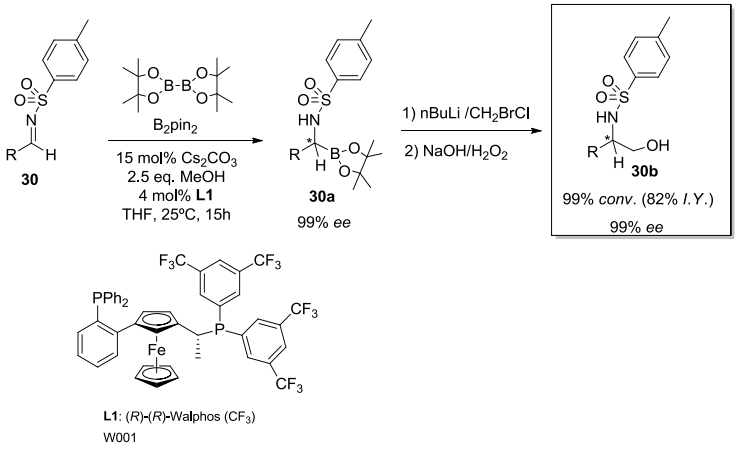
We were also interested to develop a new method to synthesize β–amino alcohols. In this context, we developed the third one-pot route based on the enantioselective organocatalytic boryl addition to tosylaldimines followed by homologation/oxidation sequence. We synthesize six different tosyladimines and discovered that only with methanol, base and the diboron reagent, we were able to carry out the selective boron addition (Scheme 8.10).



Scheme 8.10 Asymmetric organocatalytic boron addition to synthesize α–amino boronate esters.

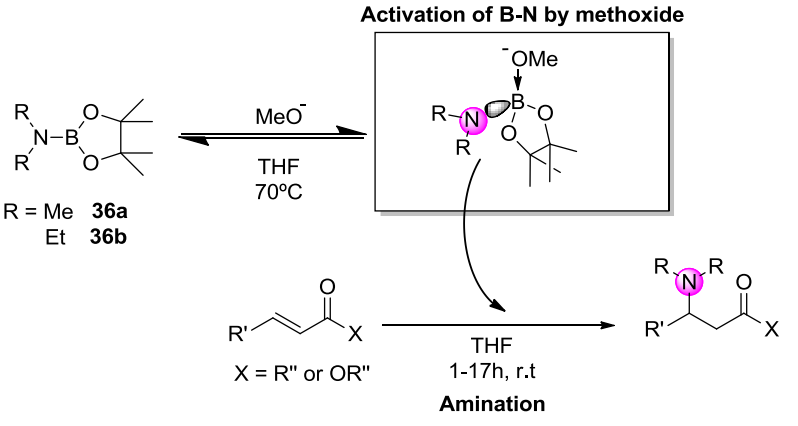
To induce high enantioselectivities in the organocatalytic borylation of tosylaldimines, chiral phosphines were screened as chiral additives with different temperatures of reaction. The best results were obtained using Walphos-type chiral ligand (up to 99% *e.e.*). By following the homologation/oxidation sequences,

we obtained the β–amino alcohol with total retention of the enantioselectivity (Scheme 8.11).



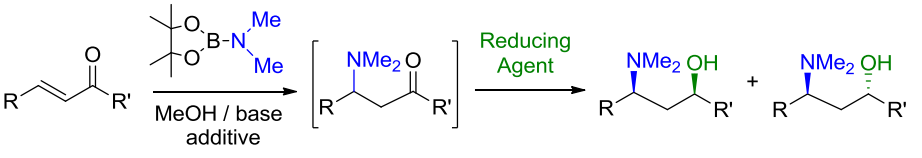
Scheme 8.11 The enantioselective organocatalytic boryl addition to C=N followed by homologation/oxidation to synthesize β–amino alcohols.

New approaches based on organocatalytic boron addition reactions were recently developed by our research group. [14] They discovered that alkoxides can interact with the diboron reagent and form a Lewis acid-base adduct facilitating the release of a boryl moiety with enhanced nucleophilic character. [15] In this context, we synthesized two aminoborane reagents to be activated by the Lewis acid-base interaction with alkoxides (Scheme 8.12) and used them in selective amination reaction of α,β–unsaturated carbonyl compounds, β-lactones and cyclic vinyl epoxides.



Scheme 8.12 Proposed activation and reactivity of aminoboranes.

Twenty substrates were screened and the β–amination provided the corresponding β–amino ketones and esters with moderate to high conversions. The in *situ* reduction of the β–amino ketones allowed us to develop the fourth one-pot sequence towards the synthesis of γ–amino alcohols based on the organocatalytic β–amination/reduction sequences. Using this methodology, four γ–amino alcohols were synthesized with moderate yields and diastereoselective control depending of the reducing agent used (Scheme 8.13).



Scheme 8.13 One pot β–amination/reduction of α,β–unsaturated ketones to synthesize γ–amino alcohols.

[1] Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

[2] Some examples are: a) Nicolaou, K. C.; Boddy, C. N. *J. Am. Chem. Soc*. **2002**, *124*, 10451. b) PrayGod, G.; Frey, A.; Eisenhut, M. *Malaria J.* **2008**, *7*, 210. c) Michael, J. P. *Natural Product Reports* **1999**, *16*, 675. d) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277.

[3] Some examples are: a) Kiyooka, S.; Suzuki, K.; Shirouchi, M.; Kaneko, Y.; Tanimori, S. *Tetrahedron Lett.* **1993**, *34*, 5729. b) Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142. c) Lait, S.; Rankic, D.; Keay, B. *Chem. Rev.* **2007**, *107*, 767.

[4] For selected examples since 2004, see: a) Stachel, S. J.; Coburn, C. A.; Steele, T. G.; Jones, K. G.; Loutzenhiser, E. F.; Gregro, A. R.; Rajapakse, H. A.; Lai, M.-T.; Crouthamel, M.-C.; Xu, M.; Tugusheva, K.; Lineberger, J. E.; Pietrak, B. L.; Espeseth, A. S.; Shi, X.-P.; Chen-Dodson, E.; Holloway, M. K.; Munshi, S.; Simon, A. J.; Kuo, L.; Vacca, J. P. *J. Med. Chem.* **2004**, *47*, 6447; b) Shimogawa, H.; Kwon, Y.; Mao, Q.; Kawazoe, Y.; Choi, Y.; Asada, S.; Kigoshi, H.; Uesugi, M. *J. Am. Chem. Soc.* **2004**, *126*, 3461; c) Gautier, A.; Mulatier, J.-C.; Crassous, J.; Dutasta, J.-P. *Org. Lett.* **2005**, *7*, 1207; f) Kaburagi, Y.; Kishi, Y. *Tetrahedron Lett.* **2007**, *48*, 8967.

[5] Some examples are: a) Li, G.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 449. b) Rudolph, P.; Sennhenn P. C.; Vlaar, C. P.; Sharpless K. B. *Angew. Chem.* **1996**, *108*, 2991. c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew Chem*. **1996**, *108*, 2995.

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[7] a) Cimarelli, C.; Giuli, S.; Palmieri, G. *Tetrahedron: Asymmety*, **2006**, *17*, 1308. b) Geng, H.; Zhang, W.; Chen, J.; Hou, G.; Zhou, L.; Zou, Y.; Wu, W.; Zhang, X. *Angew. Chem.* **2009**, *121*, 6168.

[8] a) Stühmer, W.; Heinrich, W. *Chem. Ber*. **1951**, *84*, 224. b) Perold, G.W.; Von Reiche, K. *J. Am. Chem. Soc*. **1957**, *79*, 465. c) Lunn, G. *J. Org. Chem* **1987**, *52*, 1043.

[9] a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem*. **1985**, *50*, 4052. b) Andrisano, R.; Angiolini, L. *Tetrahedron* **1970**, *26*, 5247. c) Sammaddar, K.; Konar, K.; Nasipuri, D. *J. Chem. Soc., Perkin Trans. I* .**1983**, 1449. d) Kossenjans, M.; Martens. J. *Tetrahedron. Assym.* **1999**, *10*, 3409. e) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131. f) Millet, R.; Träff, A. M.; Petrus, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2010**, *132*, 15182.

[10] Büchi, J.; Kracher, F.; Schmidt, G. *Helv. Chim. Acta*. **1962**, *45*, 729.

[11] a) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas, M. Eur. *J. Org. Chem*. **2006**, 3476. b) Ghorai, M.K.; Das, K.; Shukla, D. *J. Org. Chem*. **2007**, *72*, 5859.

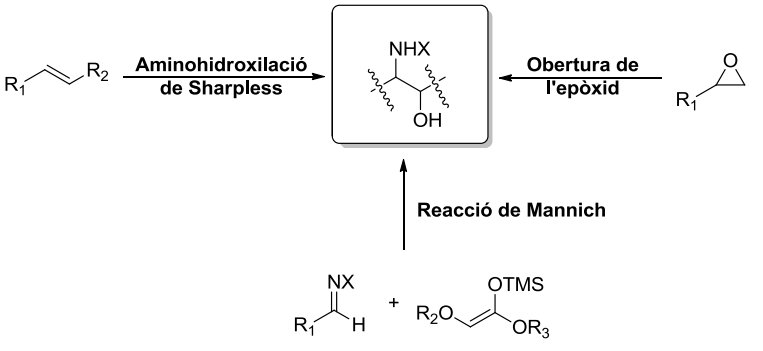
[12] Rice, G. T.; White, M. Ch. *J. Am. Chem. Soc.* **2009**, *131*, 11707.

[13] a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes, Springer, Berlin,* **1995**; p. pp 48. b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, 9704. c) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, 1840. d) Donnell, M. J. O.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *9*, 2370. e) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695. f) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, 16794.

[14] Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130.

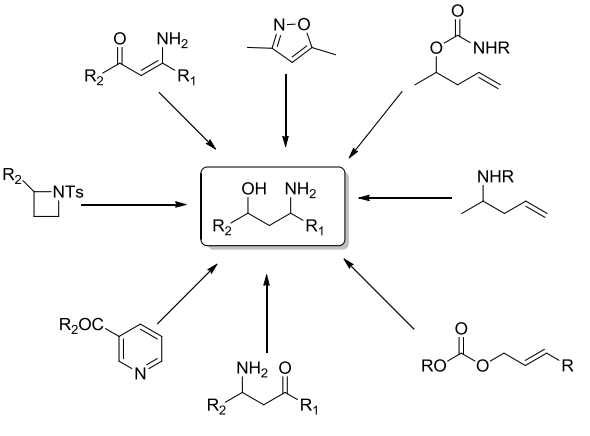
[15] a) Bonet, A.; Pubill-Ulldemolins, C; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed*., **2011**, *50*, 7158. b) Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulyás, H.; Fernández, E. *Chem.–Eur. J*., **2012**, *18*, 1121.

Els amino alcohols són estructures importants usades en la síntesis de productes naturals, [1] fàrmacs [2] i auxiliars o catalitzadors quirals aplicats en la síntesis orgànica asimètrica. [3] En l'última dècada, diferents mètodes han estat desenvolupats per la síntesi asimètrica d'aquests compostos. Els compostos β–amino alcohols es poden sintetitzar mitjançant l'obertura d'epòxids [4], amb la reacció asimètrica d'aminohidroxilació de Sharpless [5] o amb la reacció estereoselectiva de Mannich (Esquema 8.1). [6]



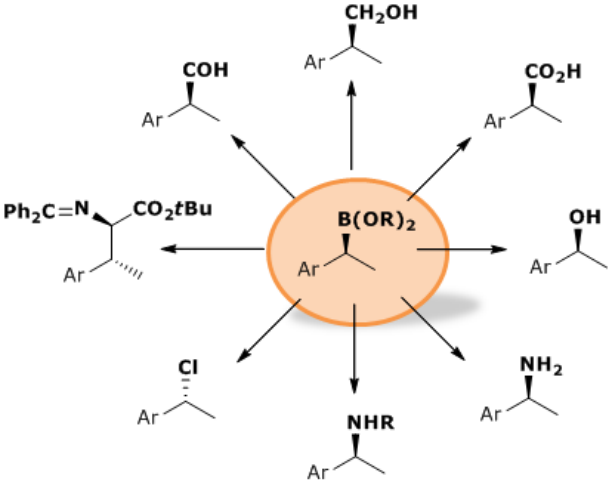
Esquema 8.1 Tres mètodes per sintetitzar els β–amino alcohols.

Els mètodes més rellevants per la síntesis dels γ–amino alcohols són les reduccions amb hidrurs de metall o amb hidrogenacions catalítiques de les enaminones, [7] isoxazolones o isoxazolines, [8] compostos β-amino carbonílics, [9] cetopiridines, [10] l'obertura de azetidines [11] o reaccions al·líliques (Esquema 8.2). [12]



Esquema 8.2 Mètodes més comuns per obtenir els γ–amino alcohols.

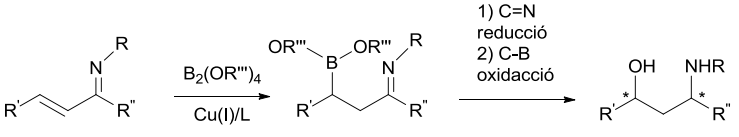
Els organoborans poden ser utilitzats com intermedis versàtils en la síntesis orgànica. [13] L'enllaç C-B es pot transformar cap als enllaços C-O, C-N, C-C i C-X mantenint la seva configuració determinada durant el procés de funcionalització (Esquema 8.3).



Esquema 8.3 Exemples de les possibles transformacions de l'enllaç C-B.

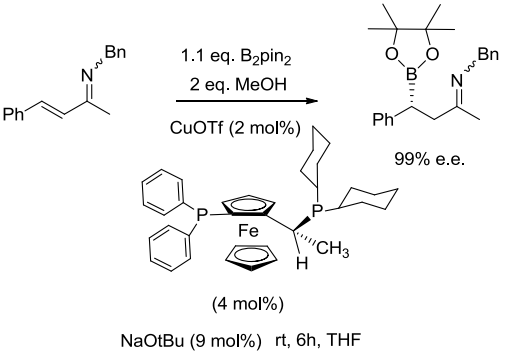
Tenint en compte els avantatges que hi ha en l'ús dels organoborans en la síntesis orgànica, quatre noves rutes "one-pot" han estat desenvolupades en aquesta tesis per sintetitzar β– o γ–amino alcohols.

La primera ruta one-pot va ser basada en la β–boració catalítica d'imines α,β–insaturades seguida per la reducció de la imina corresponent i l'oxidació de l'enllaç C-Bpin per obtenir l'estructura γ–amino alcohol desitjada (Esquema 8.4).



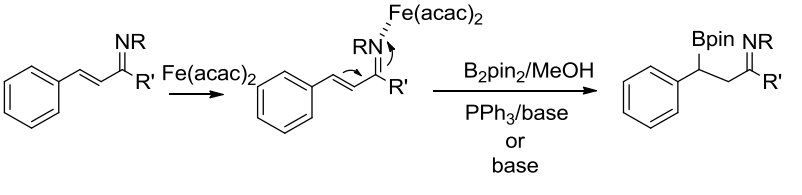
Esquema 8.4 Ruta "one-pot" composta per la β-boració catalítica d'imines α,β–insaturades seguida pels processos de reducció/oxidació.

Un gran nombre d'imines α,β–insaturades amb substituents arils en el C_β van ser sintetitzades per estudiar la β–boració catalitzada per salts de coure(I). Es van obtenir elevades conversions independentment de la naturalesa del grup imino. Quan les sals de coure(I) van ser modificades amb fosfines quirals, es van induïr enantioselectivitats elevades durant la reacció (fins a un 99% *e.e.*) (Esquema 8.5).



Esquema 8.5 Sals de coure(I) modificades amb un tipus de lligand Josiphos van induïr 99% d'enantioselectivitat en la β–boració de la 1-fenil-N-((E)-4-fenilbut-3-en-2-ilidene)metanamina.

A part del coure, l'estudi catalític de la β–boració d'imines α,β–insaturades també va ser realitzat utilitzant ferro com a metall. En aquest cas, el ferro no es el responsable de l'activació de l'agent diborat i sembla que el seu paper estigui relacionat amb l'activació del substrat mitjançant una interacció d'àcid de Lewis (Esquema 8.6).



Esquema 8.6 El paper del ferro en la β–boració d'imines α,β–insaturades.

Després de l'estudi de la β–boració catalítica de les imines α,β–insaturades, vam estar interessats en el control 1,3-diastereoselectiu de la reducció de les imines β–borades. Sis agents reductors diferents van ser utilitzats per obtenir un control total cap a la formació de l'isòmer *syn* o *anti* del γ–amino alcohol (Figura 8.1). La

reducció va ser realitzada amb l'ajuda i experta experiència del Prof. A. Whiting (Univesitat de Durham).

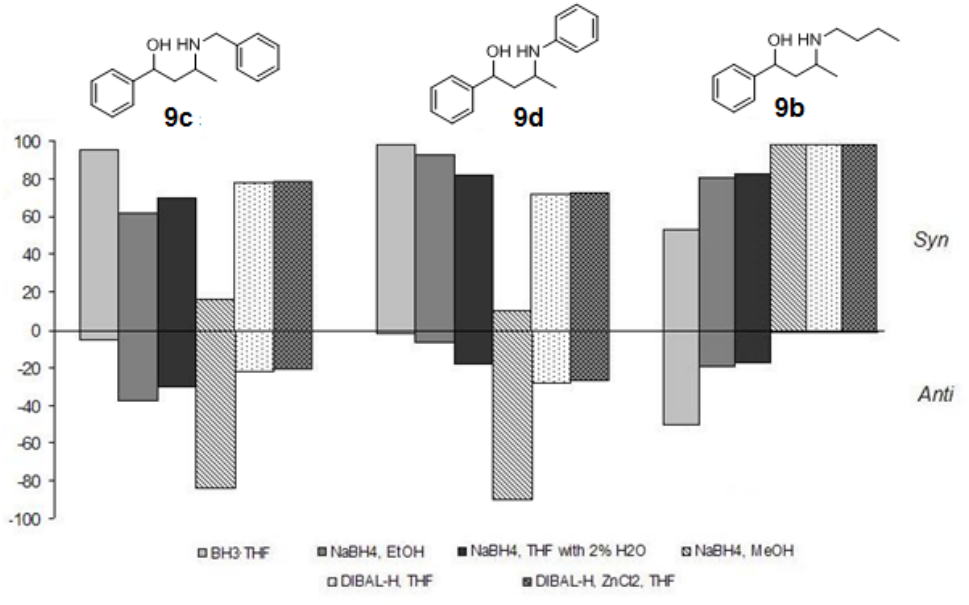
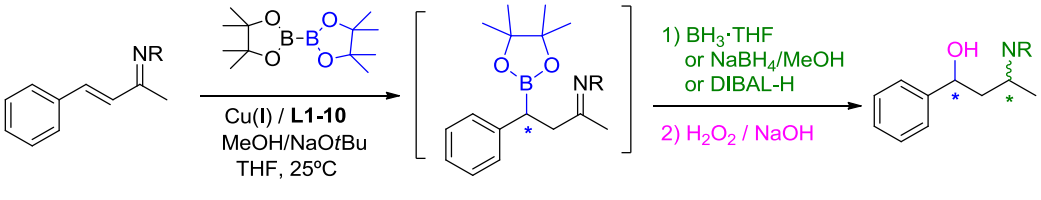


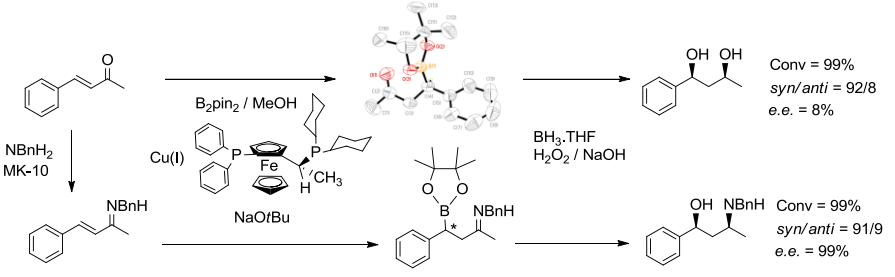
Figura 8.1 Control 1,3-diastereoselectiu en la reducció/oxidació de les imines β–borades cap a la síntesis de γ–amino alcohols.

Un cop optimitzada la reducció diastereoselectiva, vam desenvolupar la ruta one-pot estereoselectiva de la β–boració/reducció/oxidació. Les enantioselectivitats induïdes en la β–boració catalitzada per coure(I) es van conservar durant el procés de reducció/oxidació i, en conseqüència, vam ser capaços de sintetitzar γ–amino alcohols enantio- i diastereoselectius (Esquema 8.7).



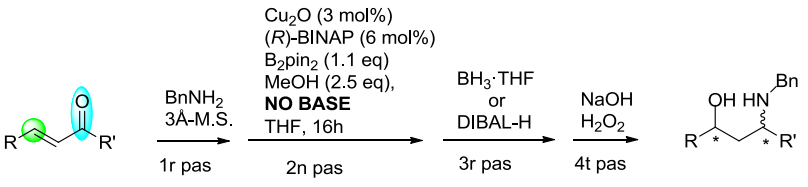
Esquema 8.7 Ruta "one-pot" estereoselectiva composta per la β–boració/reducció/oxidació de les imines α,β–insaturades per sintetitzar γ–amino alcohols quirals.

Un estudi comparatiu de la nova ruta "one-pot" es va realitzar amb cetones o imines α,β–insaturades com a substrats. Es van trobar diferències rellevants en els espectres de ressonància de bor entre les imines i les cetones β–borades. Les imines β–borades tenien senyals a camps més alts lo qual es podia explicar mitjançant una possible interacció intramolecular entre el nitrogen i el bor. Aquesta possible interacció pot influir en la diastereoselectivitat obtinguda en el procés de la reducció. Catorze estructures 1,3-difuncionalitzades van ser sintetitzades mitjançant la ruta "one-pot" β–boració/reducció/oxidació de cetones i imines activades (Esquema 8.8).



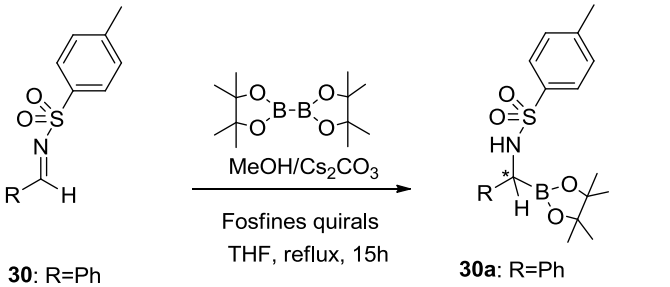
Esquema 8.8 Ruta "one-pot" β–boració/reducció/oxidació de cetones i imines activades.

La segona ruta de quatre passos "one-pot" va ser desenvolupada amb la col·laboració del grup de treball del Prof. A. Whiting (Universitat de Durham). Vam ser capaços de preparar les imines α,β–insaturades in *situ* i seguidament realitzar la seqüència de β–boració/reducció/oxidació. Aquest fet, ens va permetre poder aplicar la ruta "one-pot" a cetones α,β–insaturades al·líliques i obtenir γ–amino alcohols amb substituents al·lílics als dos costats. A més a més, vam descobrir un nou mètode en la β–boració que era asimètric, catalitzat amb coure (Cu_2O) i lligands quirals econòmicament accessibles, amb la qual no es necessitava la presència de base. Conseqüentment, vam sintetitzar nou γ–amino alcohols mitjançant aquest nou mètode "one-pot" i vam demostrar que aquesta nova metodologia pot ser aplicada de forma general per la síntesis de γ–amino alcohols quirals (Esquema 8.9).



Esquema 8.9 La formació de la imina/β-boració usant Cu_2O i (*R*)-BINAP/reducció/oxidació és la nova ruta "one-pot" per sintetitzar γ–amino alcohols quirals.

També vam estar interessats en desenvolupar una nova metodologia per sintetitzar β–amino alcohols. En aquest context, vam dissenyar la tercera ruta one-pot composta per l'addició enantioselectiva i organocatalítica del bor a tosilaldimines seguida pel procés d'homologació/oxidació. Vam sintetitzar sis tosilaldimines i vam descobrir que amb el simple ús de metanol, base i el compost diborat, es podia realitzar l'addició del bor (Esquema 8.10).



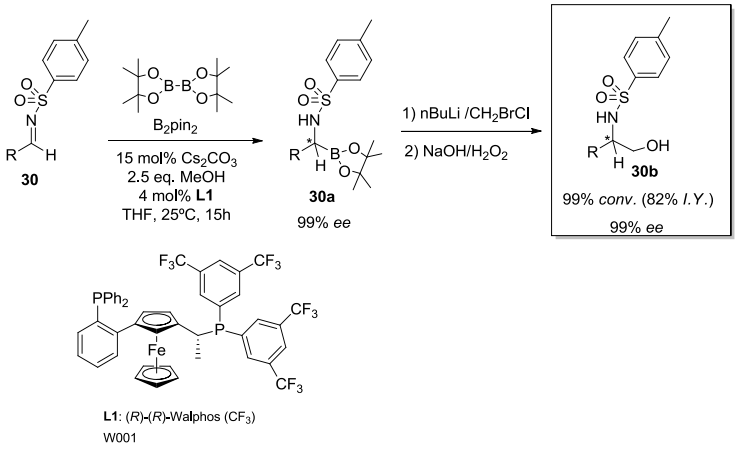
30: R=Ph
31: R=*p*-OMe-C_6H_4
32: R=*p*-F-C_6H_4
33: R=C_6H_{13}
34: R=Cy
35: R=2-Py

30a: R=Ph
31a: R=*p*-OMe-C_6H_4
32a: R=*p*-F-C_6H_4
33a: R=C_6H_{13}
34a: R=Cy
35a: R=2-Py

Esquema 8.10 Addició organocatalítica i asimètrica del bor per sintetitzar α–amino esters borans.

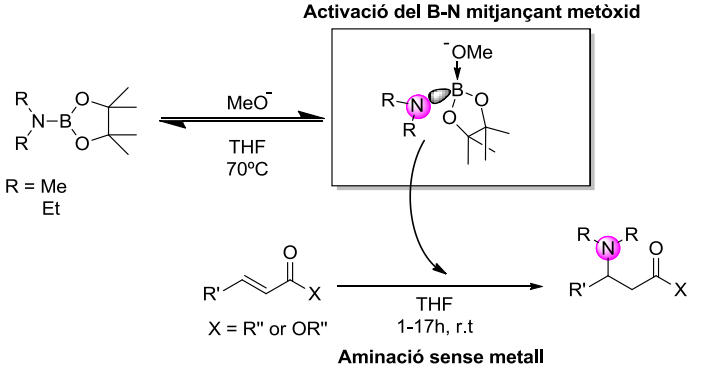
Per induir elevades enantioselectivitats en l'addició organocatalítica del bor a les tosilaldimines, es va realitzar un estudi amb diferents fosfines quirals (com additius quirals) i amb temperatures de reacció variables. Els millors resultats van ser obtinguts amb una fosfina quiral de tipus Walphos (fins a un 99% *e.e.*). Seguidament amb el procés d'homologació/oxidació, vam obtenir el corresponent

β–amino alcohol amb el mateix valor d'enantioselectivitat ja induït en el primer pas (Esquema 8.11).



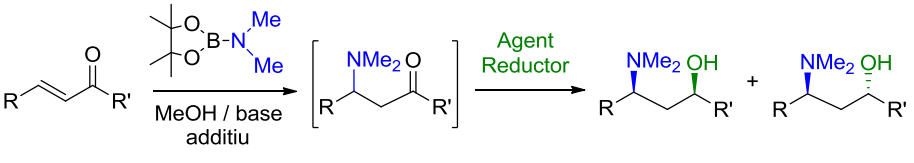
Esquema 8.11 L'addició organocatalítica del bor a C=N seguida pel procés d'homologació/oxidació permet sintetitzar β–amino alcohols quirals.

Nous descobriments basats en l'addició organocatalítica del bor han estat recentment estudiats pel nostre grup. [14] Ells van descobrir que els alcòxids poden interaccionar amb l'agent diborat i formar un adducte àcid-base de Lewis que facilita l'alliberació d'un dels grups borils amb caràcter nucleofílic. [15] Tenint en compte aquest descobriment, vam sintetitzar dos aminoborans per activar-los mitjançant la interacció amb alcòxids (Esquema 8.12) i usar-los en l'aminació selectiva de compostos carbonílics α,β–insaturats, β-lactones i epòxids vinílics cíclics.



Esquema 8.12 Activació i reactivitat proposada per l'estudi dels aminoborans.

Una vintena de substrats van ser estudiats en la β–aminació de compostos carbonílics α,β-insaturats per obtenir conversions entre moderades i elevades. La reducció in *situ* de les cetones β–aminades ens va permetre desenvolupar el quart mètode "one-pot" cap a la síntesis de γ–amino alcohols basat en la β–aminació organocatalítica/reducció. Mitjançant aquesta nova ruta "one-pot", vam ser capaços de sintetitzar quatre γ–amino alcohols amb rendiments moderats i amb controls diastereoselectius depenent de l'agent reductor usat en cada cas (Esquema 8.13).



Esquema 8.13 Ruta "one-pot" β–aminació/reducció de cetones α,β–insaturades per sintetitzar γ–amino alcohols.

[1] Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

[2] Some examples are: a) Nicolaou, K. C.; Boddy, C. N. *J. Am. Chem. Soc*. **2002**, *124*, 10451. b) PrayGod, G.; Frey, A.; Eisenhut, M. *Malaria J.* **2008**, *7*, 210. c) Michael, J. P. *Natural Product Reports* **1999**, *16*, 675. d) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277.

[3] Some examples are: a) Kiyooka, S.; Suzuki, K.; Shirouchi, M.; Kaneko, Y.; Tanimori, S. *Tetrahedron Lett.* **1993**, *34*, 5729. b) Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142. c) Lait, S.; Rankic, D.; Keay, B. *Chem. Rev.* **2007**, *107*, 767.

[4] For selected examples since 2004, see: a) Stachel, S. J.; Coburn, C. A.; Steele, T. G.; Jones, K. G.; Loutzenhiser, E. F.; Gregro, A. R.; Rajapakse, H. A.; Lai, M.-T.; Crouthamel, M.-C.; Xu, M.; Tugusheva, K.; Lineberger, J. E.; Pietrak, B. L.; Espeseth, A. S.; Shi, X.-P.; Chen-Dodson, E.; Holloway, M. K.; Munshi, S.; Simon, A. J.; Kuo, L.; Vacca, J. P. *J. Med. Chem.* **2004**, *47*, 6447; b) Shimogawa, H.; Kwon, Y.; Mao, Q.; Kawazoe, Y.; Choi, Y.; Asada, S.; Kigoshi, H.; Uesugi, M. *J. Am. Chem. Soc.* **2004**, *126*, 3461; c) Gautier, A.; Mulatier, J.-C.; Crassous, J.; Dutasta, J.-P. *Org. Lett.* **2005**, *7*, 1207; f) Kaburagi, Y.; Kishi, Y. *Tetrahedron Lett.* **2007**, *48*, 8967.

[5] Some examples are: a) Li, G.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 449. b) Rudolph, P.; Sennhenn P. C.; Vlaar, C. P.; Sharpless K. B. *Angew. Chem.* **1996**, *108*, 2991. c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew Chem*. **1996**, *108*, 2995.

[6] a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842. c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.*

2003, *125*, 338. d) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712.

[7] a) Cimarelli, C.; Giuli, S.; Palmieri, G. *Tetrahedron: Asymmety*, **2006**, *17*, 1308. b) Geng, H.; Zhang, W.; Chen, J.; Hou, G.; Zhou, L.; Zou, Y.; Wu, W.; Zhang, X. *Angew. Chem.* **2009**, *121*, 6168.

[8] a) Stühmer, W.; Heinrich, W. *Chem. Ber*. **1951**, *84*, 224. b) Perold, G.W.; Von Reiche, K. *J. Am. Chem. Soc*. **1957**, *79*, 465. c) Lunn, G. *J. Org. Chem* **1987**, *52*, 1043.

[9] a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem*. **1985**, *50*, 4052. b) Andrisano, R.; Angiolini, L. *Tetrahedron* **1970**, *26*, 5247. c) Sammaddar, K.; Konar, K.; Nasipuri, D. *J. Chem. Soc., Perkin Trans. I* .**1983**, 1449. d) Kossenjans, M.; Martens. J. *Tetrahedron. Assym.* **1999**, *10*, 3409. e) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131. f) Millet, R.; Träff, A. M.; Petrus, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2010**, *132*, 15182.

[10] Büchi, J.; Kracher, F.; Schmidt, G. *Helv. Chim. Acta*. **1962**, *45*, 729.

[11] a) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas, M. Eur. *J. Org. Chem*. **2006**, 3476. b) Ghorai, M.K.; Das, K.; Shukla, D. *J. Org. Chem*. **2007**, *72*, 5859.

[12] Rice, G. T.; White, M. Ch. *J. Am. Chem. Soc.* **2009**, *131*, 11707.

[13] a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes, Springer, Berlin,* **1995**; p. pp 48. b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, 9704. c) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, 1840. d) Donnell, M. J. O.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *9*, 2370. e) Crudden, C. M.; Edwards, D. *Eur. J. Org.*

Chem. **2003**, 4695. f) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, 16794.

[14] Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130.

[15] a) Bonet, A.; Pubill-Ulldemolins, C; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed*., **2011**, *50*, 7158. b) Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulyás, H.; Fernández, E. *Chem.–Eur. J*., **2012**, *18*, 1121.

Chapter 9: Appendix

9.1 Publications within this thesis

Cristina Solé, Elena Fernández.
"Catalytic β-boration/oxidation of 1-azadienes"
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Current Organic Chemistry, **2010**, *14*, 2531.

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"Organocatalytic versus Iron-Assisted β–boration of Electron-Deficient Olefins."
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"Highly Enantio- and Diastereoselective Synthesis of γ–Amino Alcohols from α,β-Unsaturated Imines through a One-Pot β-Boration/Reduction/Oxidation Sequence."
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"Catalytic 1,3-Difunctionalization of Organic Backbones via a Highly Stereoselective, One-Pot, Boron Conjugate-Addition/Reduction/Oxidation Process."
Chemistry: an Asian Journal, **2011**, *17*, 14248.

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"Asymmetric synthesis of α–amino boronate esters via organocatalytic pinacolboryl addition to tosylaldimines."
Chemical Communications, **2012**, *48*, 3769.

Cristina Solé, Amadeu Bonet, Andre H. M. de Vries, Johannes G. de Vries, Laurent Lefort, Henrik Gulyás, Elena Fernández.
"Influence of Phosphoramidites in Copper-Catalyzed Conjugate Borylation Reaction."
Organometallics, **2012**, 31*, 7855.*

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"Asymmetric organocatalytic diboration of alkenes."
Org. Biomol. Chem., **2012**, *10*, 6621.

Adam D. J. Calow, Andrei S. Batsanov, Elena Fernández, Cristina Solé, Andrew Whiting.
"Novel transformation of α,β-unsaturated aldehydes and ketones to γ-amino alcohols or 1,3-oxazines via a 4 or 5 step, one-pot sequence."
Chemical Communications, **2012**, *48,* 11401.

Adam D. J. Calow, Cristina Solé, Andrew Whiting, Elena Fernández.
"Base-free β–boration of α,β–unsaturated imines catalysed by Cu_2O with concurrent enhancement of asymmetric induction."
ChemCatChem, **2013**, *in press*.

Cristina Solé, Elena Fernández.
"The pull-pus effect of B in aminoboranes towards selective amination."
Manuscript in preparation.

9.2 Congresses and Scientific meeting

Attendance

15th IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS)
Glasgow, 26th-30th of July, 2009

ICIQ Summer School
Institute of Chemical Research of Catalonia (ICIQ), Tarragona, 19th-23th of July 2010

Poster

17th International Symposium on Homogeneous Catalysis
Poznán, Poland, 4th-9th of July, 2010
Poster contribution: "Efficient catalytic β–boration of 1-azadienes"

Oral communication

VI Trobada de Joves Investigadors dels Països Catalans
Valencia, 1st-2nd of January 2010
Catalan Society of Chemistry
Oral Comunication: "Addicions catalítiques conjugades de bor cap a la formació selectiva de β–boril carbonils i imines" *(best oral communication in catalysis)*

Euroboron5
Heriot-Watt University, Edinburgh, UK, 29thAugust-2nd of September, 2010
Flash-poster presentation: "Efficient catalytic β–boration of 1-azadienes"

XXVIII Reunión del GEQO
Punta Umbría, Huelva, 7th-10th of September 2010
Flash-poster presentation: "Una aproximación eficaz en la reacción de β–boración catalítica de 1-azadienos"

XXXIII Reunión Bienal RSEQ
València, 25th-28th of July 2011
Flash-poster presentation: "Synthesis of 1,3-difunctionalized moleculs from α,β–unsaturated compounds through a one-pot β–boration/reduction/oxidation sequence"

IME Boron XIV
Niagara Falls, Canada, 11th-15th of September 2011
Flash-poster presentation:"Catalytic 1,3-difunctionalization of orgànic backbones via one-pot boron conjugate addition/reduction/oxidation process"

9.3 Research Abroad

a) **"Synthesis of γ–amino alcohol through one-pot sequence: Study of the reduction step "**

March 210 to June 2010

Internship at the University of Durham (UK); Final Project for M.Sc. degree

Supervisor: Dr. Andrew Whitting

b) **"Synthesis of Benzoxaboroles as biological active compounds"**

February 2012 to August 2012

Internship at Anacor Pharmaceuticals Inc. (Palo Alto, California, USA)

Supervisor: Vincent Hernández, Director of the Chemistry Department

"The real purpose of running isn't to win a race, it's to test the limits of the human heart." (Bill Bowerman)

Seguint la mateixa filosofia, no trobo millor manera de finalitzar…

"The real purpose of research isn't to publish results, it's to learn more about the unknown."

(Cristina Solé)