SELECTIVE POLYFUNCTIONAL SYNTHESIS THROUGH ORGANOBORON COMPOUNDS

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DOCTORAL THESIS

Supervised by
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Departament de Química Física I Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

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FAN CONSTAR

Que el treball titulat "Selective polyfunctional synthesis through organoboron compounds", que presenta Enrico La Cascia per a l'obtenció del Títol de Doctor, ha estat realitzat sota la nostra direcció en els centres esmentats i que compleix els requeriments per a poder optar a la Menció de Doctor Internacional

Tarragona, 1 de setembre de 2016

La directora de la tesi

Prof. Maria Elena Fernández

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A special thanks goes to my family which has supported me both economically and emotionally during these years abroad.

In the end, I would like to spend few words for my girlfriend Alison. Many thanks for supporting me and staying close to me even though the difficult moments.

Sharing our lives is the best experience of my life! xx

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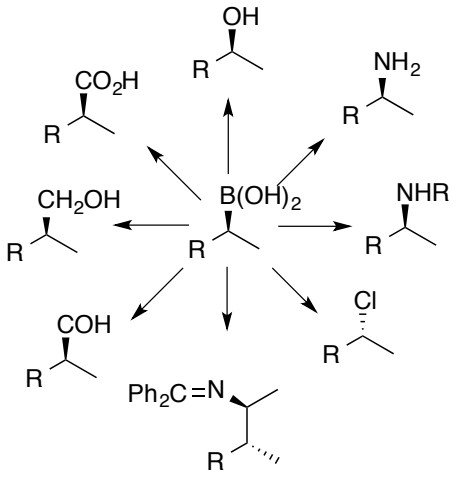
Chapter 1.

1. Introduction on organoboron chemistry.

In the last decades, the scientific community has demonstrated the great synthetic potential of organoboron compounds and, in particular, how this class of molecules are useful and versatile due to their reactivity, stability and accessibility.[1,2]
Regarding the nature of C-B bond, a wide range of useful transformations can be performed in order to introduce functionalities to obtain products with high control of chemo-, regio-, and stereoselectivity (Scheme 1.1).

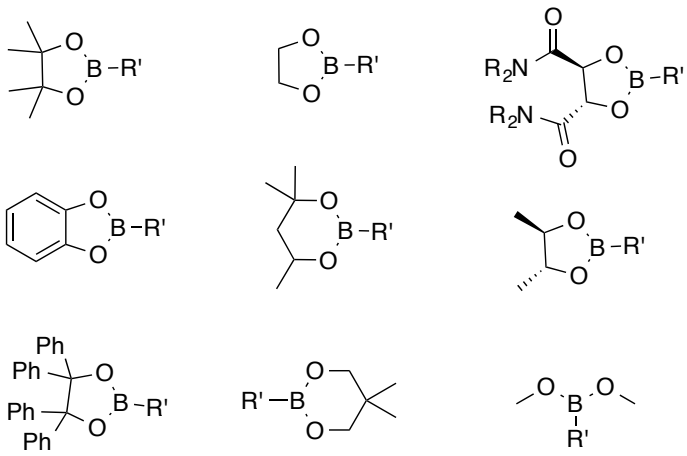


Scheme 1.1 Some examples of C-B bond transformation.

The most versatile class of organoboranes are certainly organoboronic esters, which have important chemical properties. For instance, they are very stable due to the partial donation of the lone pair of electrons of the oxygen atoms into the empty *p*-orbital of the boron atom making the latter less Lewis acidic. From the practical

point of view, this sort of interaction allows an easier manipulation of these chemicals.

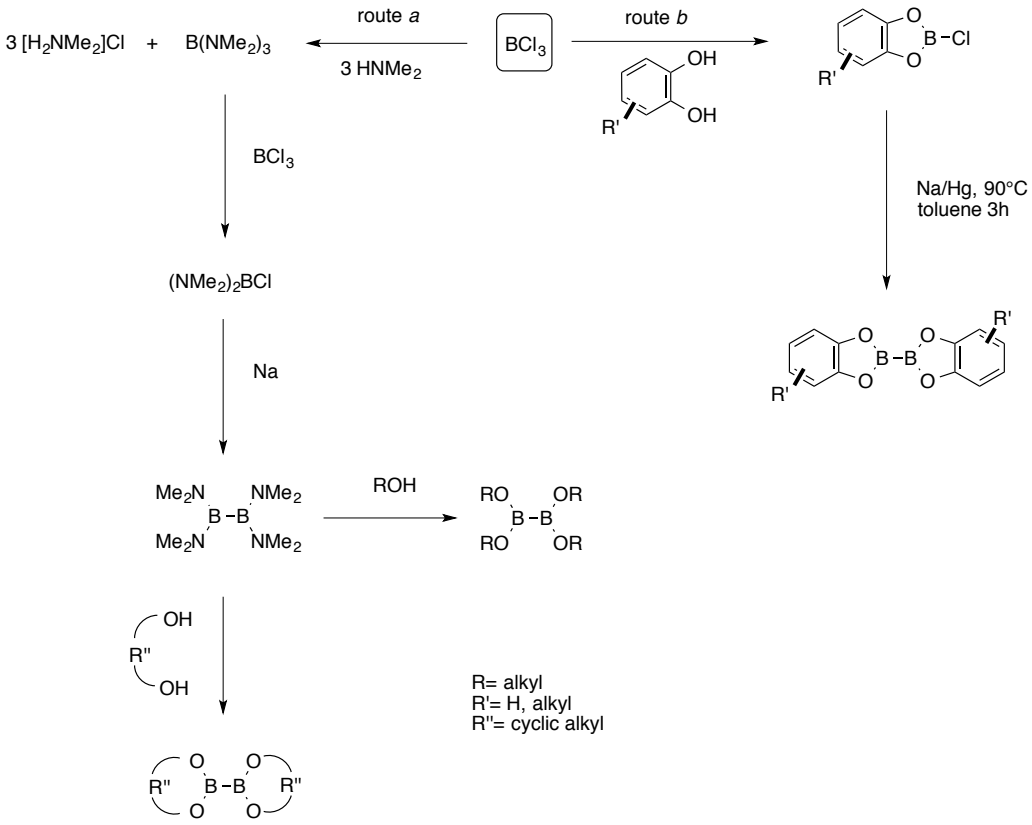
The stability of these compounds is mostly related to their structure (Scheme 1.2) where bulky, aliphatic and cyclic organoboronates show less chances to get hydrolysed.[3]



Scheme 1.2 Structures of some organoboronic esters.

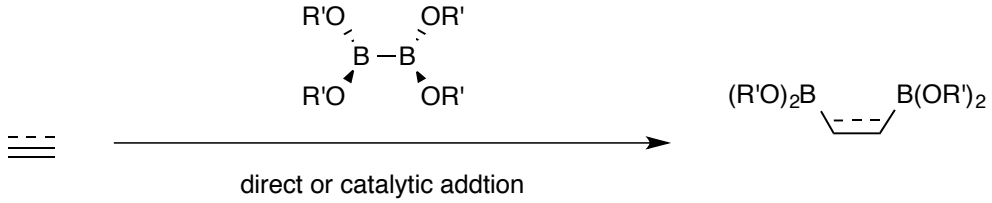
It is important to highlight that diboron compounds are nowadays strategically used in the synthesis of organoboronic esters.

Diboron compounds are commercially available with a reasonable price or alternatively they are easy to synthesize. One of the best methodology toward their synthesis was established by Noth[4] and improved by Marder[5] and Srebnik[6a] involving the formation of a tris(alkylamino)borane as intermediate (Scheme 1.3, route *a*). Another procedure was developed by Hartwig and co-workers[6b] which is based on a reductive homocoupling of halocatecholboranes (Scheme 1.3, route *b*).



Scheme 1.3 Methodologies for the synthesis of diboron compounds.

Concerning the reactivity of diboron compounds, diboration reaction is the most common reaction occurring on unsaturated organic substrates to synthesize organodiboronic esters.[7] (Scheme 1.4)



Scheme 1.4 Addition of diboron compounds to unsaturated substrates.

1.2 Introduction on Cu-mediated β-boration reaction of α,β-unsaturated carbonyl compounds.

Diboron reagents have been used in β-boration (or boron conjugate addition BCA) with an icreasing success.[8] This reaction involves diboron species such as, [B_2pin_2 (pin = $OCMe_2CMe_2O$) (**1**), B_2cat_2 (cat = 1,2-$O_2C_6H_4$) (**2**), B_2neop_2 (neop = $OCH_2CMe_2CH_2O$) (**3**), B_2hex_2 (hex = $OC(Me)_2CH_2CH(Me)O$) (**4**) (Fig 1.1) which undergo Michael-type conjugate addition to an electro deficient olefin, affording the 1,4-addition adduct which after work-up, yields the β-borated product through hydrolysis or methanolysis (Scheme 1.5).[8]

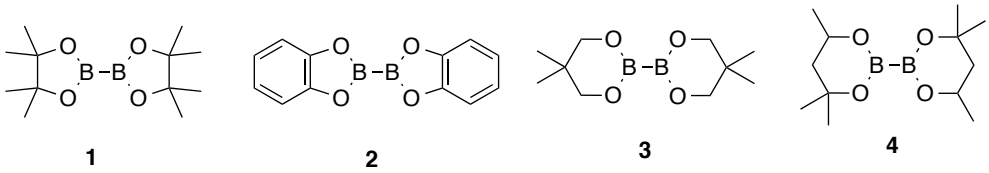
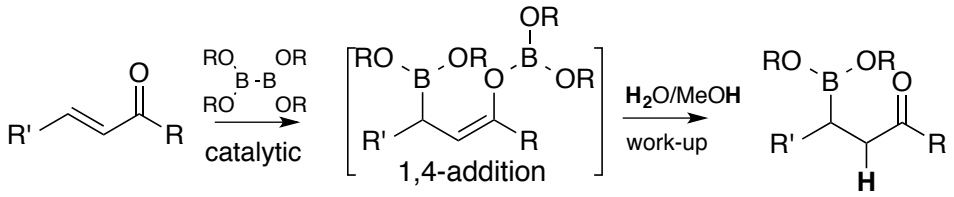


Figure1.1 Diboron compouns B_2pin_2 **1,** B_2cat_2 **2**, B_2neop_2 **3**, $B_2(hex)_2$ **4.**

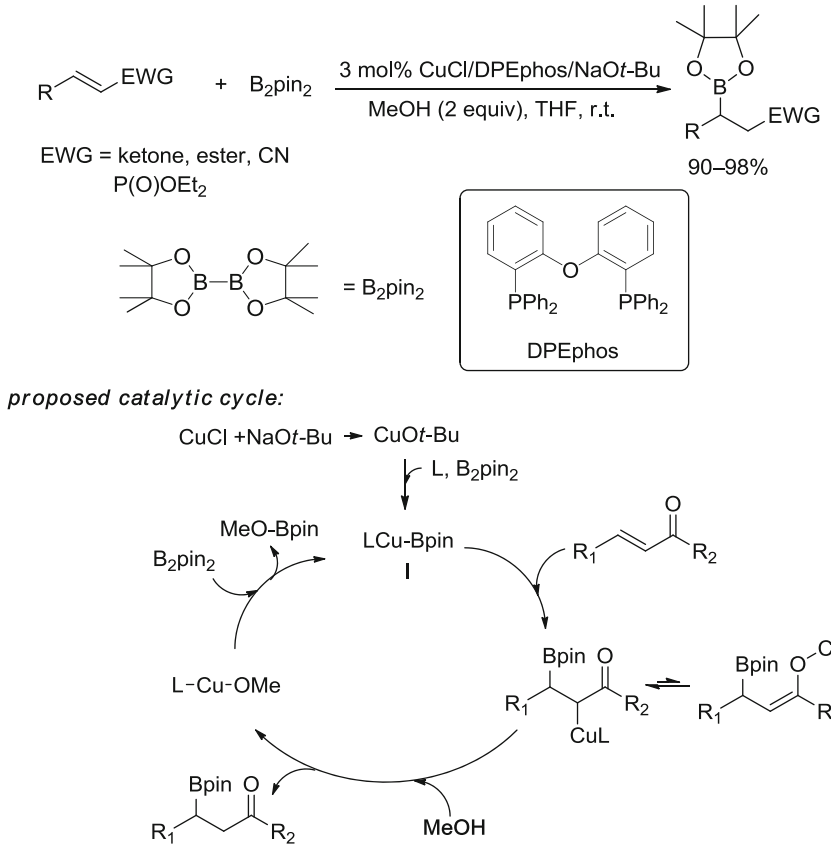


Scheme 1.5 β-Boration of α,β-unsaturated carbonyl compounds using diboron compounds.

A series of catalytic processes have been developed for borylation with a large variety of acceptors and catalysts based on transition metals and organocatalysts.

Marder, Norman and co-workers provided the initial report of racemic β-boration carried out with Pt in 1997.[9] Other groups subsequently introduced racemic β-

boration using catalytic systems based on Cu (2000)[10, 11] and Rh (2002).[12] However, an asymmetric variant of the reaction did not appear until Yun's report in 2006,[13] which expanded the substrate scope under copper catalysis in the presence of methanol and included the first example of asymmetric β-boration of an α,β-unsaturated nitrile (Scheme 1.6). A more detailed study of the asymmetric β-boration of α,β-unsaturated esters and nitriles was reported in 2008 by the same group.[14]



Scheme 1.6 β-boration of α,β-unsaturated acceptors in the presence of methanol.

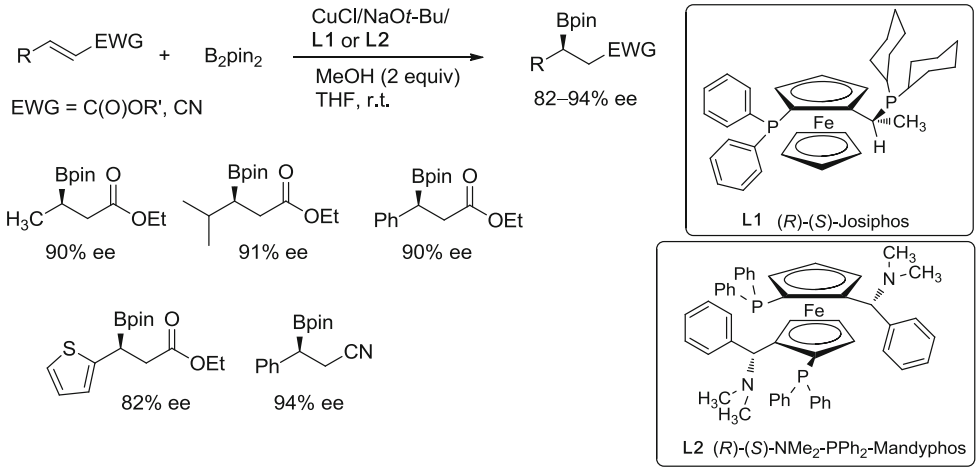
The active species in the catalytic system is a phosphine-bound-copper-boryl moiety (**I**), and its addition to a α,β-unsaturated carbonyl compound generates an alkyl copper-enolate intermediate which is cleaved by methanol. The following step

is the formation of the protonated product and the copper alkoxide species. This latter regenerates the active copper boryl catalyst by reaction with the diboron reagent (Scheme 1.6).

Some theoretical calculations supporting Yun's mechanism have been performed by Marder et al.[15] They found that 3,4 addition of Cu-B to the activated substrate occurs with subsequent isomerization of the *O*-copper enolate. This can provide a facile σ-bond metathesis with the diboron reagent in the case of enones but such isomerization does not occur for α,β-unsaturated esters. In this case a protonolysis of the C-bound copper enolate by an alcohol is mandatory because of a low activation energy barrier.

Even though Yun and co-workers reported that the addition of an alcohol accelerate the reaction rates, the alcohol additive can cause nonselective background reactions via copper species non-coordinated by the chiral ligand. The use of optimal ligands with high binding affinities for copper and high selectivities is necessary to achieve high enantioselectivities.

A general protocol for the asymmetric β-boration of acyclic α,β-unsaturated esters and nitriles using CuCl/NaO*t*-Bu as a catalytic system and in the presence of 2 eq. of methanol, requires the use of a chiral ligand. After an intense screening it has been demonstrated that the use of Josiphos-type ligand **L1** and Mandyphos **L2** coordinated to Cu(I) could provide high values of enantioselectivity (84-92% *ee*). In addition the ligands were not dependent from the structures of the starting material resulting in similar *ee* values (Scheme 1.7).

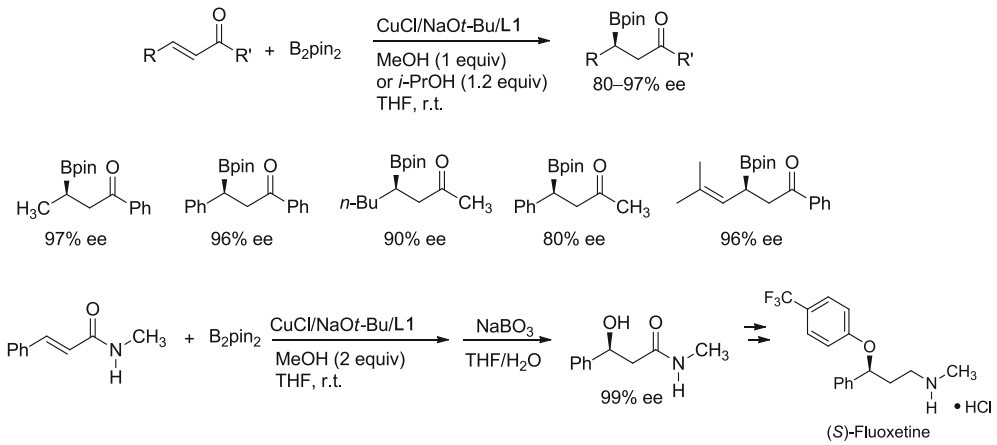


Scheme 1.7 Asymmetric β-boration of α,β-unsaturated esters and nitriles using **L1** and **L2** as chiral ligands.

It has also been reported that the adduct Cu(I)-Josiphos-type ligand **L1** can promote the β-boration of acyclic β-monosubstituted enones,[16] amides[17] (Scheme 1.8).

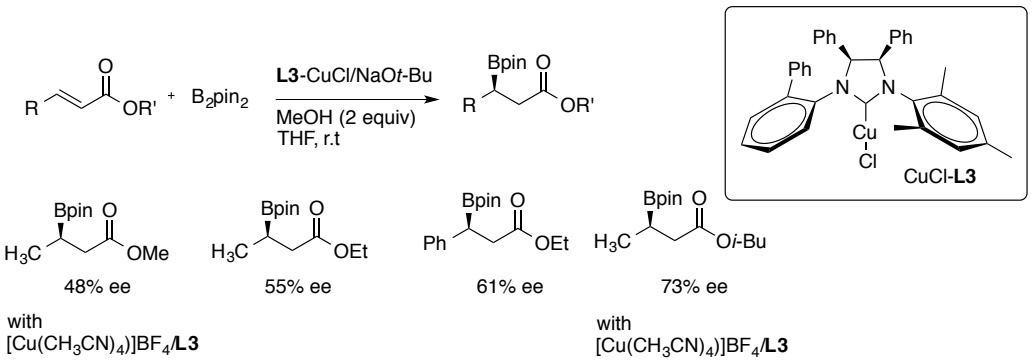
Regarding the β-boration of acyclic enones, it was carried out by using 1 eq. of methanol or even the bulkier isopropanol to reduce nonselective background reactions which could compromise the *ee* values. The Cu(I)-**L1** catalytic system provided very high values of enantioselectivity (up to 97%) for a wide range of enones. When a similar approach was used for the β-boration of α,β-unsaturated amides, the relative borylated products showed that the formal synthesis of (*S*)-fluoxetine could be carried out (Scheme 1.8).[17]

N-Heterocyclic carbene (NHC) ligands are strong σ-donors and they showed their suitability for many transition metal-catalyzed transformations.[18-20]



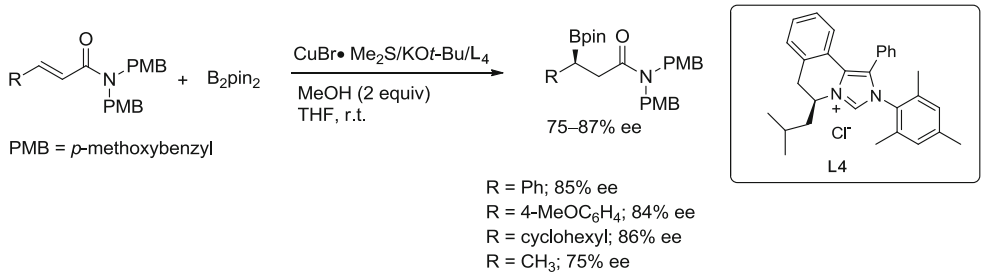
Scheme 1.8 Asymmetric β-boration of enones and amides with Cu(I)-**L1**.

Due to their strong affinity for metals, chiral NHCs are very good ligands for asymmetric β-boration. In 2009, Fernández and co-workers reported that chiral NHC-copper catalyst can performe the β-boration of α,β-unsaturated esters and cinnamaldehyde.[21] The reaction proceeded with good conversion using either **L3**-CuCl or [Cu(CH_3CN]BF_4/**L3** as precatalyst, in the presence of methanol, but only modest enantioselectivities were observed (Scheme 1.9).



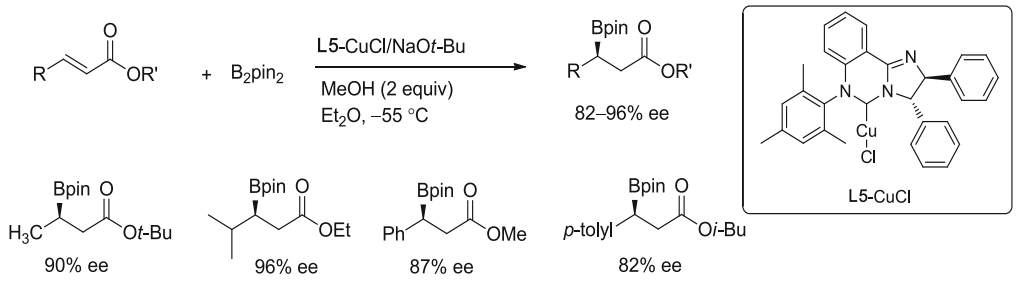
Scheme 1.9 Enantioselective β-boration of α,β-unsaturated esters using NHC (**L3**) ligangs in Cu(I) catalytic precursors.

Several chiral NHCs with different scaffolds have been synthesized and tested in Cu(I)-catalyzed asymmetric β-boration since the first report by Fernández et al. Cu-NHC catalysts are generally reactive enough to cover less electrophilic unsaturated esters and amides. In 2010, Hong and co-workers reported the β-boration of α,β-unsaturated amides using isoquinoline-based chiral diaminocarbene (**L4**) as a ligand.[22] The new isoquinoline-based Cu-NHC catalyst displayed good enantioselectivities for borylation of *N,N*-di(p-methoxybenzyl)amides, but the catalyst resulted in decreased enantioselectivities (53–78% *ee*) for nitrile, ester, Weinreb amide, and dialkyl amide derivatives of cinnamic acid (Scheme 1.10).



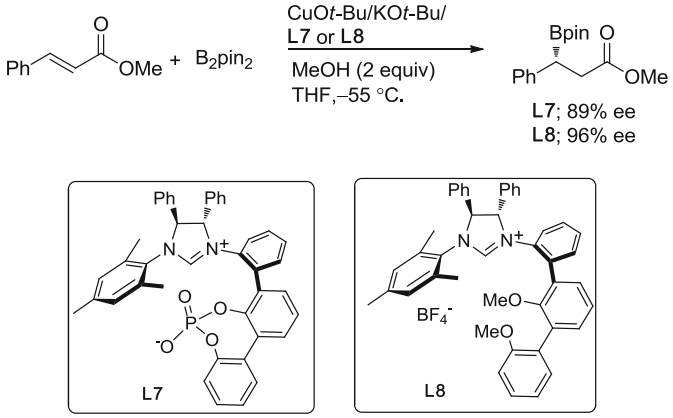
Scheme 1.10 Asymmetric β-boration of α,β-unsaturated amides using Cu-NHC (**L4)** as catalytic system.

MaQuade and co-workers also reported that a chiral 6-membered Cu-NHC complex, formed from (**L5**-CuCl), is effective for the β-boration of α,β-unsaturated esters (Scheme 1.11).[23] The catalyst was highly active for esters, and its selectivity was optimized at -55 °C. The catalyst was sensitive to the ester moiety and β-substituent, giving methyl cinnamate in the highest *ee* (87% *ee*) among a series of cinnamates (R=Ph, R'= methyl, ethyl, isobutyl). The opposite trend was observed for the crotonate series, in which bulky *tert*-butyl crotonate gave the best result (90% *ee*). Other substrate types, such as amides and ketones, were not investigated with the same catalyst.



Scheme 1.11 Asymmetric β-boration of α,β-unsaturated esters using Cu-NHC (**L5)** as catalytic system.

Sawamura and co-workers demonstrated the efficiency of copper modified with sophisticated N-carbene ligands towards the enatioselective β-boration of methyl cinnamate.[24] The active catalytic species was generated *in situ* with CuO*t*-Bu and **L7** or **L8** with a *m*-terphenyl-based moiety affording the products in 89% and 96% *ee* at -55 °C, respectively (Scheme 1.12). However, this catalytic system was not investigated for other type of substrates.

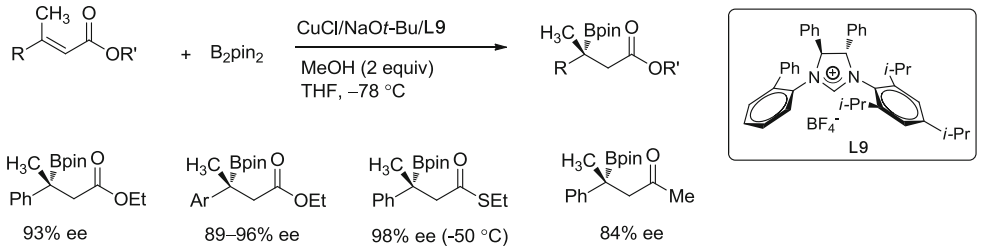


Scheme 1.12 Cu-NHC (**L7** or **L8)** catalyze the β-boration of methyl cinnamate.

The efficiency of the β-boration reaction is usually affected by the nature of the electron-withdrawing group on the α,β-unsaturated acceptor (ketone > esters > amides) and steric hindrance around the reaction site (from no substitution to β-

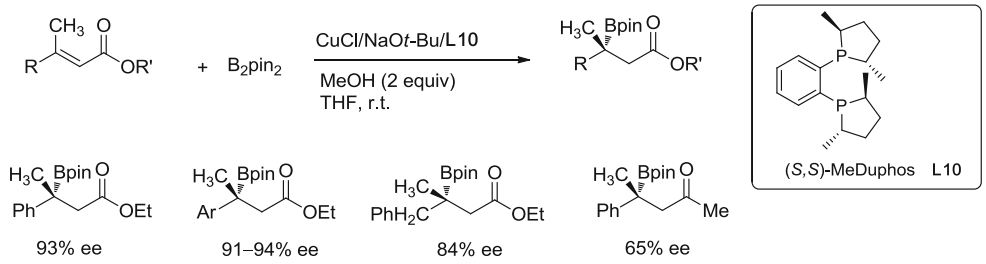
mono- or β,β-disubstitution). For this reason, the formation of quaternary chiral stereogenic centers from β,β-disubstituted α,β-unsaturated acceptors remains a challenging transformation.

In 2010, Hoveyda and co-workers developed an enatioselective β-boration of β,β-disubstituted esters, ketones and thioesters using a monodentate Cu-NHC/(**L9**) complex.[25] The reactions were efficient and delivered products with high enantioselectivity up to 98% *ee* at low temperature (-50 or -78 °C) (Scheme 1.13). Unsaturated thioesters showed higher enantioselectivity (89-98% *ee*) than unsaturated esters, but enones were less enatioselective with this protocol.



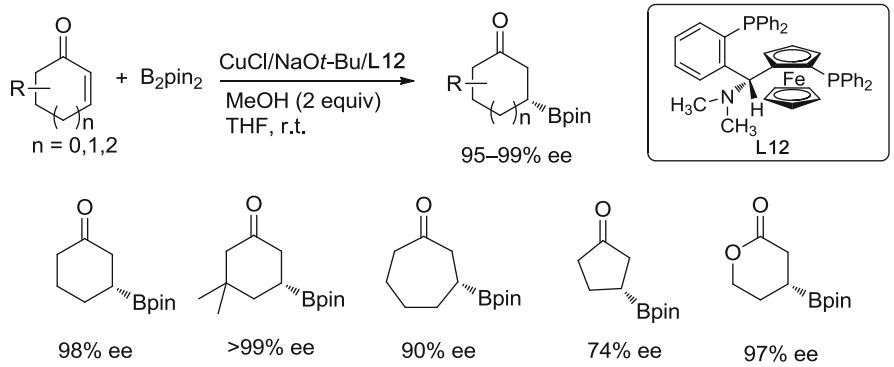
Scheme 1.13. Enantioselective β-boration of β,β-disubstituted ketones, esters and thioesters with Cu-NHC (**L9**).

At the same time in 2010, Yun and co-workers reported the enantioselective β-boration of β,β-disubstituted α,β-unsaturated esters using a bidentate phosphine (**L10**)[26] (Scheme 1.14) as a chiral ligand coordinated to Cu(I), overcoming in this way the limits of reactivity found with the Cu(I)/**L1** complex. The reaction occurring on ethyl ester (93% *ee*) provided higher *ee* values than enones or *t*-butyl ester (88% *ee*) indicating that the Cu(I)/**L10** complex is sensitive to the size and nature of the electron-withdrawing groups.



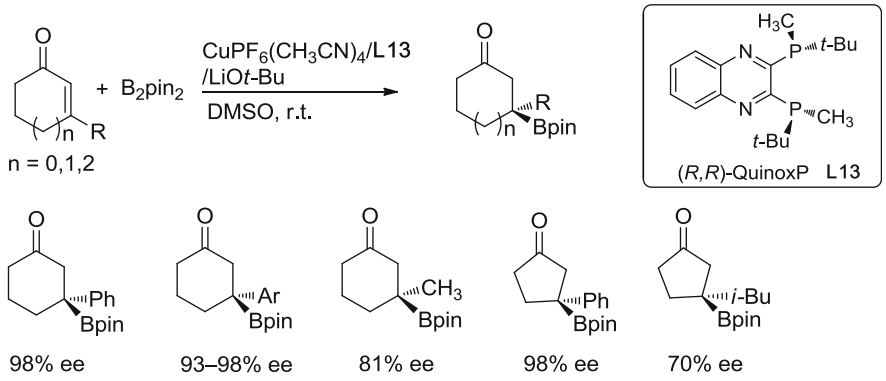
Scheme 1.14. Enantioselective β-boration of β,β-disubstituted ketones and esters using Cu(I)/**L10** catalyst.

The same group also reported the first example of enantioselective β-boration of cyclic α,β-unsaturated acceptors using a Cu(I)-Taniaphos (**L12**) catalyst.[27] This complex could provide very high values of enantioselectivity (up to 99% *ee*) for the corresponding β-borated 6- and 7-membered rings products (cyclic ketones and esters) but lower *ee* were detected in the case of 5-membered rings like cyclopentenone (Scheme 1.15).



Scheme 1.15 Enantioselective β-boration of cyclic enones and esters using Cu(I)/**L12** catalyst.

Shibasaki and co-workers reported that Cu(I)/QuinoxP*(**L13**) complex could catalyze the enantioselective β-boration of β-substituted cyclic enones in DMSO.[28] High *ee* values (93-98% *ee*) were reported for β-aryl-substituted cyclohexenone and cyclopentenone, but β-methyl- or isobutyl-substitued cyclic compounds gave lower enantioselectivities (70-85% *ee*), (Scheme 1.16). In this protocol no alcoholic additives were used, so the resulting boron enolates could be used for further aldol addition reactions.

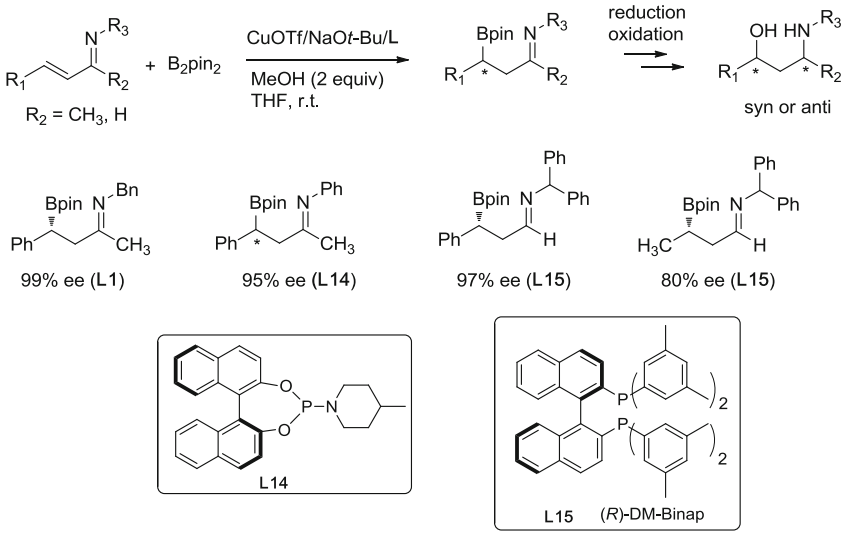


Scheme 1.16. Enantioselective β-boration of β-substituted cyclic α,β-unsaturated enones using Cu(I)/QuinoxP*(**L13**) complex.

1.3 Introduction on Cu-mediated β-boration reaction of α,β-unsaturated imines.

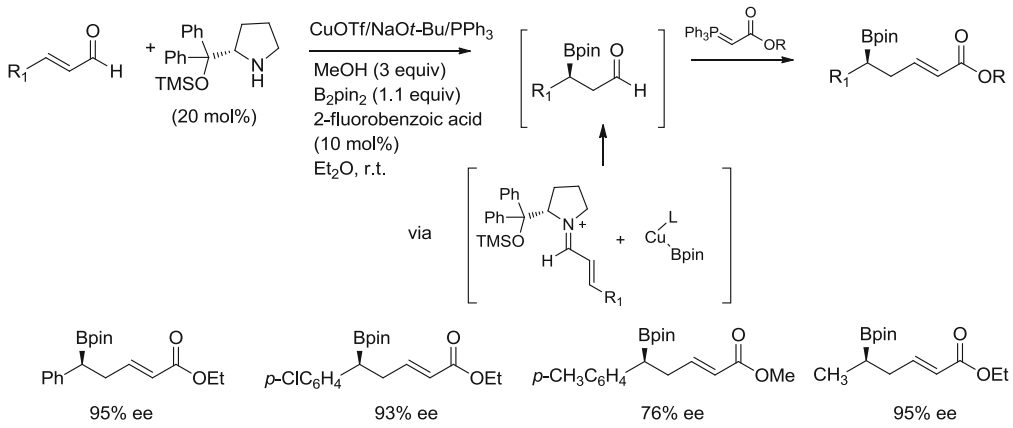
An early report by Solé and Fernández, demonstrated that CuCl would activate B_2pin_2 and add selectively the Bpin unit to α,β-unsaturated ketimines and oximes.[29] After this stimulating work, Fernández, Whiting and co-workers published a series of works regarding the asymmetric copper catalyzed β-boration of α,β-unsaturated ketimines and aldimines.[30-31] Some examples with good values of enantioselectivity are reported (Scheme 1.17). Normally, the *N*-substituent of the

imine moiety remarkably affected the enantioselectivity of each catalytic system. Cu(I) modified with chiral phosphines like **L1** or **L15** provided good values of *ee*. The resulting β-borated imines could be further transformed into the corrisponding γ-amino alcohols with high diasteroselectivity through a one-pot reduction and oxidation protocol. The study was extended to the β-boration of α,β-unsaturated imines with Cu(I) modified by chiral phosphoramidites, through an interesting method supported by DMS.[32]



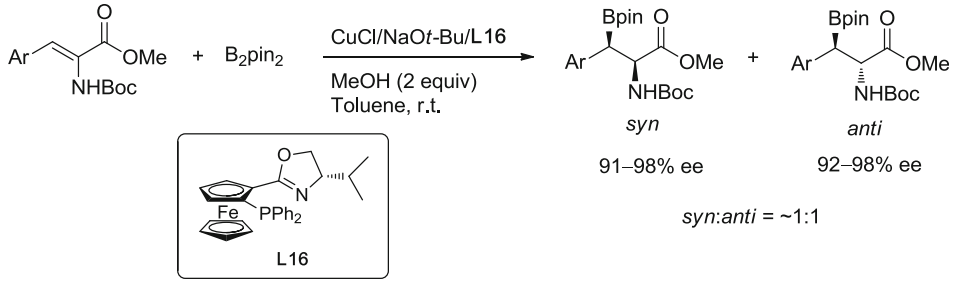
Scheme 1.17 Enantioselective copper catalyzed β-boration of α,β-unsaturated imines with Cu(I)-phosphines and Cu(I)-phosphoramidites.

In 2011, Córdova and co-workers reported an enantioselective synthesis of homoallylboronates through the enantioselective β-boration of enals and sequential Wittig reaction.[33] The chiral iminium intermediate which induces the enantiocontrol of the copper catalyst was detected by ^{1}H NMR and HRMS. Amine-catalyzed chiral iminium ion formation from enals and copper-catalyzed activation of diboron reagents were combined in this investigation to achieve enantioselective borations (Scheme 1.18).



Scheme 1.18 One-pot enantioselective β-boration of homoallylboronates.

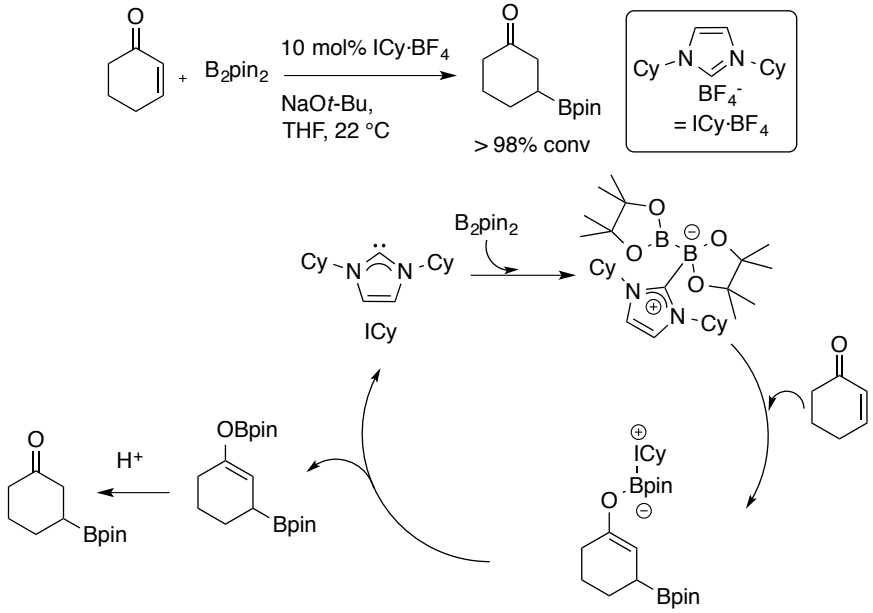
In 2014, Lin and co-workers reported the enatioselective β-boration of substituted α-aminoacrilates esters using a Cu(I)/**L16** complex.[34] The enatioselectivity of the process was excellent (up to 96% *ee*) but a poor diasteroselectivity was achieved (≈1:1) (Scheme 1.19). This methodology provided a new route for a facile synthesis of β-hydroxy-α-amino acids.



Scheme 1.19 Enantioselective β-boration of substituted α-aminoacrilates esters using Cu(I)/**L16** complex.

1.4 Introduction of organocatalytic-mediated β-boration reaction of α,β-unsaturated compound.

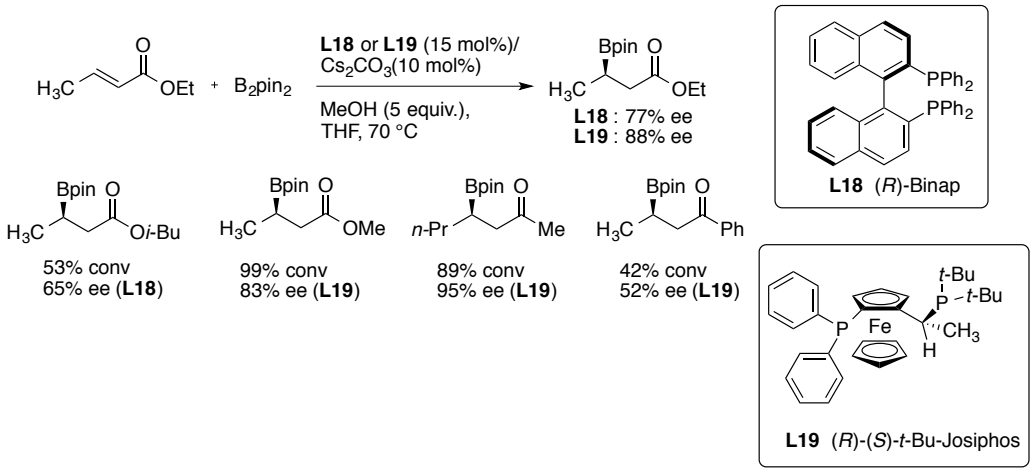
The sp^2-sp^3 reactivity of diboron compounds without any transition metal catayst has been studied recently. Hoveyda and co-workers were the first to develop a non-metal catalyzed β-boration reaction on cyclic and acyclic α,β-unsaturated ketones and esters in a racemic version (Scheme 1.20).[35] They proposed a model where bis(pinacolato)diboron was activated by the coordination of a nucleophilic carbene (NHC). This complex then reacted with the Michael acceptor substrate and generated a 1,4-diborated product that developed into the β-borated ketone after hydrolysis.



Scheme 1.20. Racemic metal-free β-boration of α,β-unsaturated carbonyl compounds using NHC.

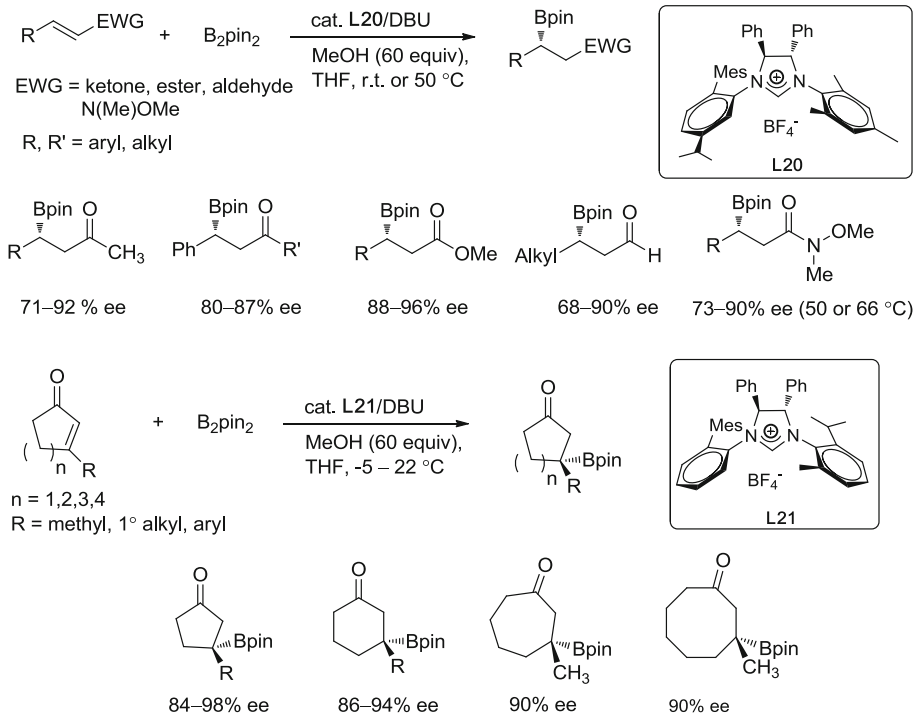
In 2010, Fernández and co-workers reported the first metal-free asymmetric β-boration using a chiral bidentate phosphine, as additive, at 70 °C, (Scheme 1.21).[36] After a ligand screening, Binap (**L18**) and *t*-Bu-Josiphos (**L19**) displayed higher

conversion for ethyl crotonate (> 99%) with 77% and 88% of *ee* values, respectively. When bulkier isobutyl crotonate where used both conversion and enantioselectivity decreased. The protocol demonstrated to be efficient for enones but the transformation was dependent to the nature of the substituents. In general **L19** resulted better than **L18** in terms of enantioselectivity.



Scheme 1.21. Asymmetric metal-free β-boration of α,β-unsaturated esters and ketones using **L18** and **L19**.

Hoveyda and co-workers carried out further intensive studies on asymmetric metal-free β-boration of α,β-unsaturated carbonyl compounds catalyzed by chiral imidazolium salts (**L20** and **L21**).[37] The use of chiral NHC additives 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and a base facilitated the asymmetric addition of Bpin moiety to α,β-unsaturated carbonyl compounds in the presence of MeOH (Scheme 1.22).



Scheme 1.22 Enantioselective β-boration of α,β-unsaturated carbonyl compound using imidazolium salts **L20** and **L21**.

Substrates like esters, ketones and aldehyde were suitable acceptors providing very high values of *ee* (up to 96%) with **L20**. However, in some cases the full conversion was not achieved. In particular, the less reactive Weinreb amides needed higher temperatures (55-60 °C) and longer time of reaction to afford the corresponding products with a reasonable conversion (67-98 %).

Concerning the β-boration of cyclic acceptors, a slightly different catalyst **L21** was used affording the desired β-borated products with good conversion and enantioselectivity.[38]

1.5 Introduction on β-boration of activated olefins in water.

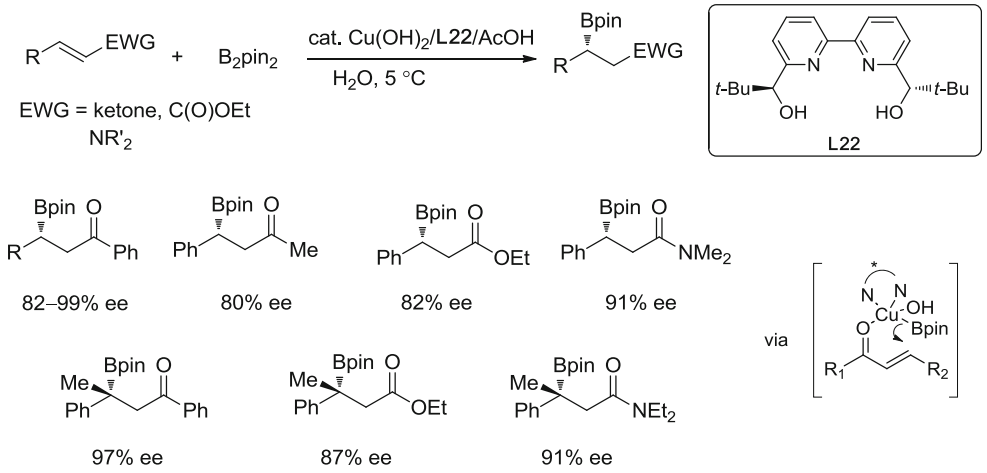
Water is an environmentally friendly solvent and it has been used for efficient organic transformation.[39] Since the β-boration usually requires the presence of an alcohol to promote the reaction, many efforts have been made to employ water as suitable solvent.

Yun and co-workers developed a ligandless copper(I)-catalyzed β-boration of α,β-unsaturated ketones, esters and amides by using a catalytic amount of copper(I) or copper(II)oxide in combination with NaO*t*-Bu.[40]

Also Santos and co-workers reported that $CuSO_4 \cdot 5H_2O$ and picoline could catalyze the β-boration of α,β-unsaturated esters and ketones in water.[41]

Kobayashi and co-workers reported in 2012 the first enantioselective β-boration of α,β-unsaturated carbonyl compounds and nitriles in water by using a chiral bidentate ligand (2,2'-bipyridine) **L22** to modify the $Cu(OH)_2$ catalyst.[42,43]

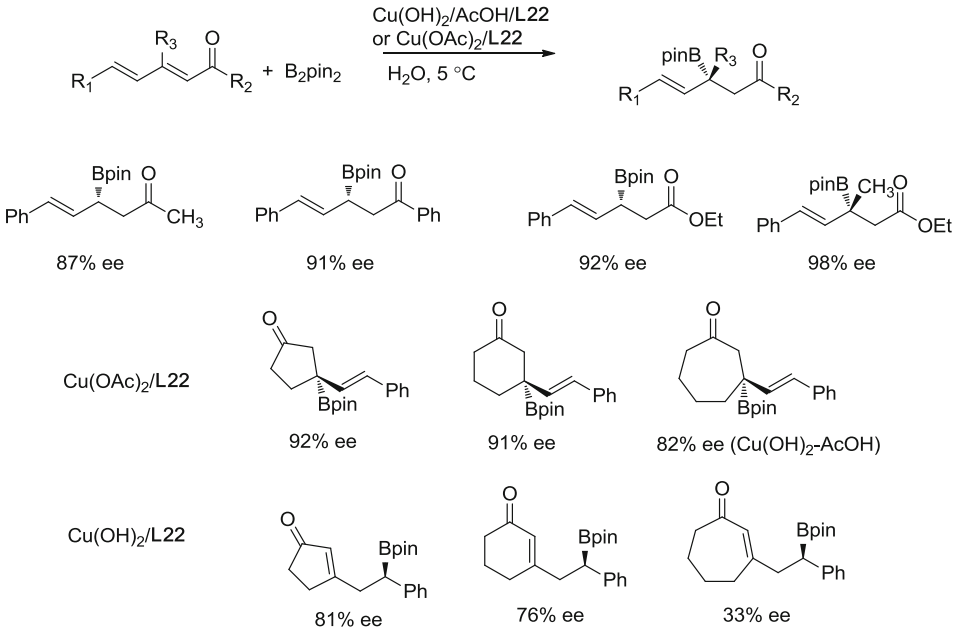
In that context, α,β-unsaturated ketones, including cyclic enones afforded the desired products in high yields and enantioselectivities (Scheme 1.23).



Scheme 1.23 Cu-catalyzed enantioselective β-boration of α,β-unsaturated acceptors in water.

The same group reported the β-boration of dienones and dienoesters in water.[44] Both $Cu(OH)_2$ and $Cu(OAc)_2$ were able to catalyze the β-boration of α,β,γ,δ-unsaturated dienones and dienoesters showing a strong preference for 1,4-addition over 1,6-addition.

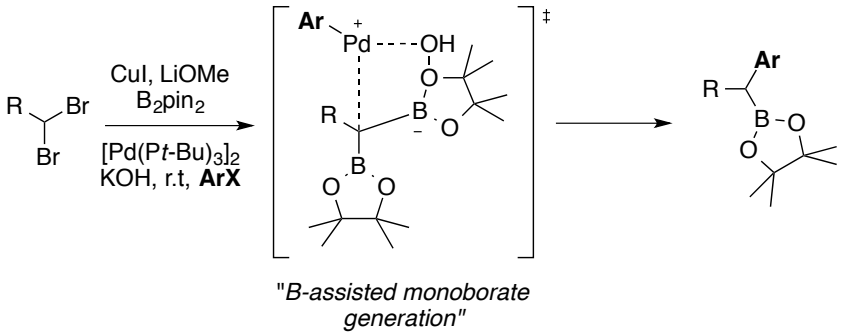
An interesting control of the regioselectivity was observed for 5-, 6-, and 7-membered ring cyclic dienones. The use of a combination of $Cu(OH)_2$/AcOH or $Cu(OAc)_2$ resulted in an exclusive formation of the 1,4-adduct with high enantioselectivity while the use $Cu(OH)_2$ as catalyst gave a 1,6-addition product with moderated enantioselectivity (Scheme 1.24).



Scheme 1.24 Enantioselective boration of α,β,γ,δ-unsaturated carbonyl compounds.

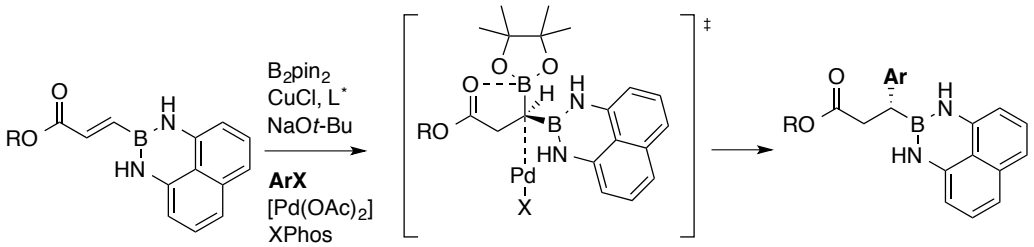
1.6 General introduction to the synthesis of 1,1-diboryl- and 1-boryl, 1-silyl-compounds.

1,1-Diborylalkanes are gaining success among organic chemists since Shibata and co-workers reported in 2010 that two consecutive cross-coupling can be performed with complete regio- and chemoselectivity, even at room temperature.[45] This new approach is based on the protection-free selective cross-coupling on a multisubstituted sp^3 carbon and is achieved through the adjacent B atom in 1,1-diborylalkanes (Scheme 1.25).



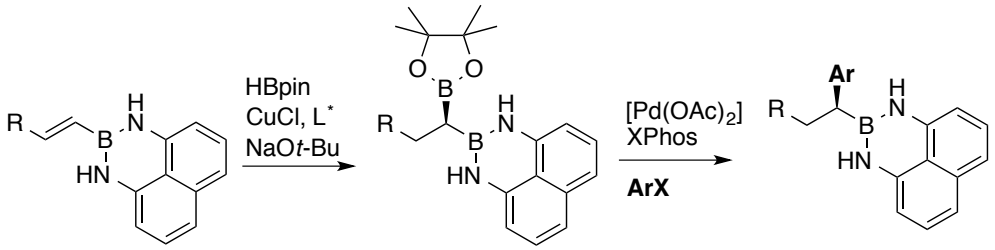
Scheme 1.25 Protection-free cross-coupling on a multisubstituted sp^3-carbon.

If a chiral ligand is used, the reaction occurs through a stereochemical-determining transmetallation process with inversion of the configuration.[46] When a second cross-coupling is performed, an unsymmetrical diarylated compound is formed from the simple 1,1-dibromoalkanes.[47] The group of Hall[48] reported the unsymmetrical synthesis of 1,1-diborylakanes through the asymmetric borylation of β-boronylacrilates assisted by copper (Scheme 1.26).



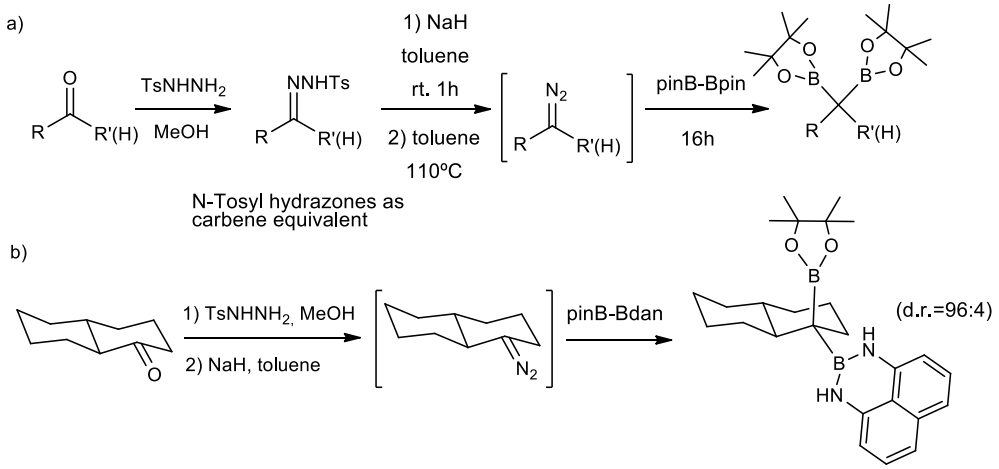
Scheme 1.26 Copper-catalyzed synthesis of unsymmetrical 1,1-diborylalkanes.

Also the group of Yun and co-workers developed a copper-catalyzed synthesis of 1,1-diborylakenes through the asymmetric hydroboration of borylalkenes (Scheme 1.27).[49] The two synthetic routes have in common the presence of the C-Bdan moiety in the starting material and in both cases the Bpin moiety is introduced in a stereodefined way by the copper catalyst modified with chiral ligands.



Scheme 1.27 Synthesis of unsymmetric1,1-diborylalkanes through copper-catalyzed hydroboration.

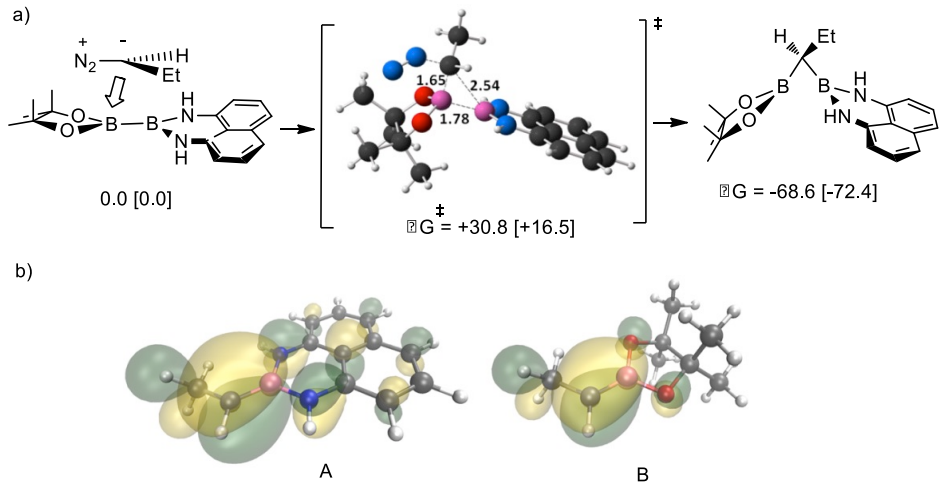
Alternative methods to generate 1,1-diborated alkanes, where both C-B bonds are simultaneously formed, have been originally attributed to the Pt-catalysed diborylation of diazoalkanes with Bpin-Bpin[50] but more recently to the metal-free carbon insertion of N-tosylhydrazones into Bpin-Bpin[51] (Scheme 1.28a) and Bpin-Bdan (Scheme 1.28b).[52]



Scheme 1.28 Metal-free 1,1-diboration of ketones and aldehydes through tosylhydrazones/diazocompounds.

Employing N-tosylhydrazones derived from aldehydes and ketones could be directly diborated and diastereoselection was achieved when employing diazo precursors possessing diastereotopic p faces. A plausible mechanistic pathway has been elucidated by DFT calculations to understand the heterolytic cleavage of Bpin-Bdan and $CH_3(H)CN_2$ as model diazoalkane. Scheme 1.29 summarizes the outcome of these calculations and the transition state for the formation of the two carbon-boron bonds that indicate the occurrence of a concerted, yet asynchronous mechanism with a free energy barrier of 30.8 kcal. mol^{-1}. As the nucleophilic diazo carbon attacks at the electron deficient boron of the Bpin moiety, the 1,2-boron migration of the Bdan moiety occurs to yield the 1,1-diboron intermediate and concomitant release of the nitrogen (Scheme 1.29a).[52] In this scenario, diastereoselection can be achieved due to a combination of repulsive 1,3-diaxial from substrate and 1,2-*cis* interactions with the diboron reagent. It has been possible to establish a selective C-Bpin functionalisation from the enriched diastereoselective *gem*-diborated products, via alkoxide assisted selective

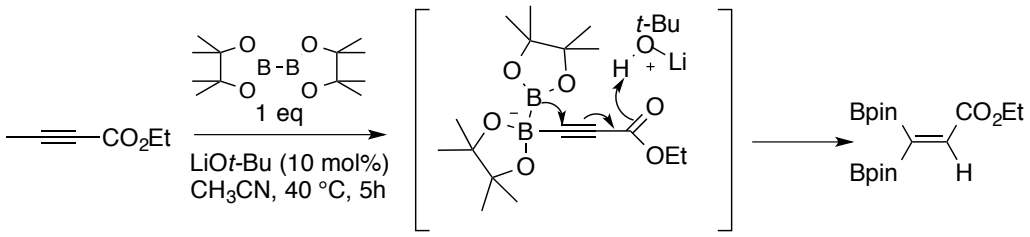
deborylation of Bpin versus Bdan (using 3eq KO*t*-Bu at 0º). Computational analysis of the reactivity of 1,1-diborylalkanes with alkoxides using $CH_3(H)C(Bpin)(Bdan)$ and MeO^- as model substrates indicated the formation of a stable Lewis acid-base adduct with preferential interaction of MeO^- and Bpin, followed by deborylation. The stabilization of the carbanion using the α-Bdan moiety is reflected in the HOMO orbital, which shows strong delocalization of the carbanion p-type electron density into the π-channel of the Bdan moiety (Scheme 1.29, A). According to NBO analysis, the alternative carbanion using the α-Bpin fragment (Scheme 1.29, B) supports a less negative charge (-0.14e) than the Bdan fragment (-0.21e). Thus, selective functionalization of the Bpin position is expected.[52]



Scheme 1.29 a) Mechanistic proposal via DFT studies for metal-free 1,1-diboration of diazocompounds with Bpin-Bdan, b) Relative stabilization of the carbanion using the α-Bdan moiety (A) and α-Bpin moiety (B).

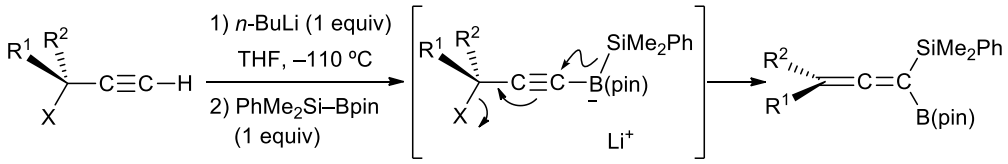
The 1,1-diboration could also be initiated by deprotonation of terminal alkynes with LiO*t*-Bu to form a lithium acetylide and *t*-BuOH. When lithium acetylide reacts with B_2pin_2 forms an alkynyl borate intermediate, that suffers

the migration of the terminal boryl moiety to the *sp*-hybridised carbon atom of the alkyne group associated with protonation of the carbonyl oxygen atom to generate an allenol that is eventually isomerised to the final 1,1-diborated functionalised alkene (Scheme 1.30).[53] Interestingly the two germinal boron substituents of the 1,1-diborylalkene could be differentiated and transformed in a stepwise manner.



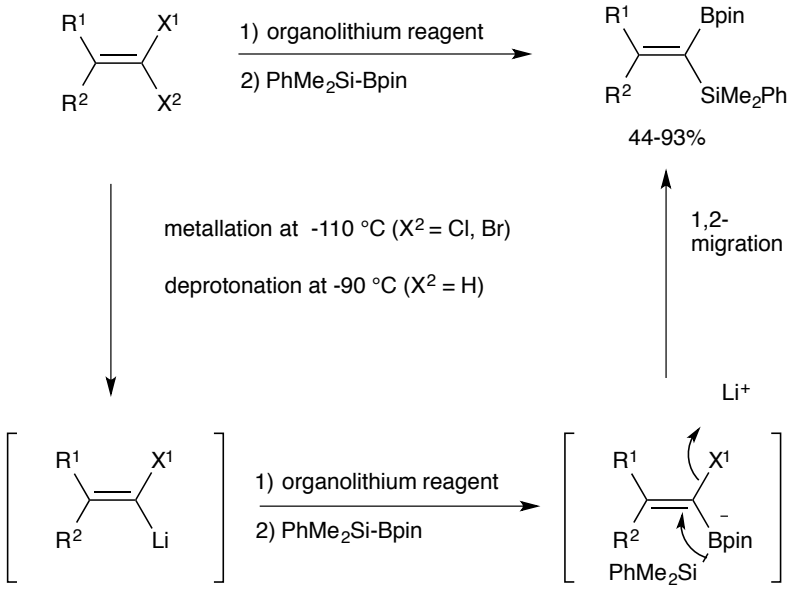
Scheme 1.30 Stereoselective *anti*-diboration of alkynoates and 1,1-diboration of propiolates, propiolamides and 2-ethynyazoles.

Similarly, treatment of 3-choloro- or 3-alkoxy-1-alkynes with butyllithium at -110 °C generates the corresponding alkynyllithium, which react with $PhMe_2SiBpin$ to produce 1-boryl-1-silylallenes through the 1,2-migration with S_N2' substitution from the borate complex (Scheme 1.31).[54]



Scheme 1.31 Synthesis of 1-boryl-1-silylallenes via *gem*-silylborylation of an acetylenic carbon.

Hiyama and Shimizu later reported several 1,2-migration reactions of $PhMe_2SiBpin$ and *in situ*-generated carbenoid species (Scheme 1.32).[55,56] The 1-halo-1-lithioalkenes that were generated by metalation of 1,1-dihaloalkenes or deprotonation of 1-haloalkenes react with silylborane to form boronate intermediate. Subsequent 1,2-migration gave the 1-boryl-1-silyl-1-alkenes in a stereospecific manner.



Scheme 1.32 Synthesis of 1-boryl-1-silyl-1-alkenes from 1,1-dihaloalkenes and silylborane through 1,2-migration.

1.7 Scope of the thesis and objectives.

In this thesis we wanted to apply the organoboron chemistry to synthesize compounds with synthetic interests.

The first part mainly covers the application of the β-boration reaction of α,β-unsaturated imines towards the synthesis of γ-amino alcohols.

Objective 1: We search for an organocatalytic route towards the β-boration of α,β-unsaturated imines.

Objective 2: We tried to develop a challenging total synthesis of Tramadol based on a new methodology.

The aim of the last part is base on the study of insertion of Me_3Si-Bpin into ketones to perform suitable intermediates towards selective tetrasubstituted olefins.

Objective 3: Study of the synthesis of (*Z*)-Tamoxifen.

1.8 References

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Chapter 2.

β-Boration of α,β-unsaturated imines generated "in situ" towards the synthesis of enantioenriched γ-amino alcohols.

2.1 Scope of the art on γ-amino alcohols.

From the chemical point of view, amino alcohols are characterized by containing both amino and alcohol functional groups, providing, in this way, an interesting class of difunctional compounds.

Amino alcohols can be classified according to the relative position of the two functional groups as a α-, β-, or γ-amino alcohols (Figure 2.1).[1]

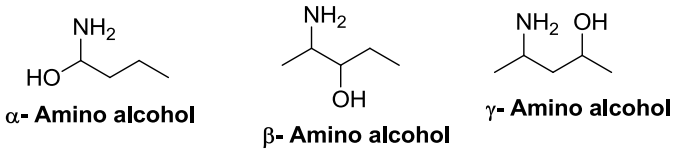


Figure 2.1. Structure of amino alcohols.

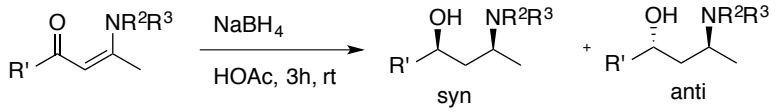
While α-amino alcohols are the less stable due to the presence of the two functional groups on the same carbon, β- and γ-amino alcohol are important building blocks with interesting applications.

The need to prepare new synthesis of γ-amino alcohols is justified by their real interest in pharmacology. The γ-amino alcohols are found in several antibiotics and other biologically active natural products.[2]

Interestingly, the synthesis of γ-amino alcohols has efficiently been performed from diols[3], hydroxazols[4], lactams[5] and lactones.[6] However, the most direct reduction of 1,3-difunctionalised unsaturated compounds, containing N and O, is more synthetically convenient. Between the reduction of 1,3-difunctionalised

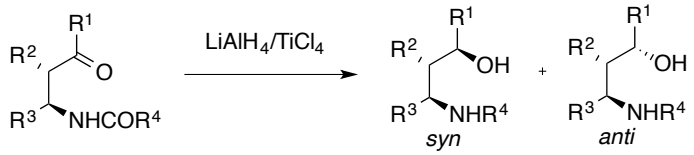
substrates it can be highlighted the reduction of β-hydroxy oximes[7] or β-enamino ketones.[8-12]

Remarkably, the reduction of β-enamino ketones with $NaBH_4$ in glacial acetic acid provides the γ-amino alcohol in 70%-98% yield with diastereomeric excesses from 44%-90% in favour of the *syn* product (Scheme 2.1).[13]



Scheme 2.1 Diastereoselective synthesis of γ-amino alcohols through the reduction of β-enamino ketones.

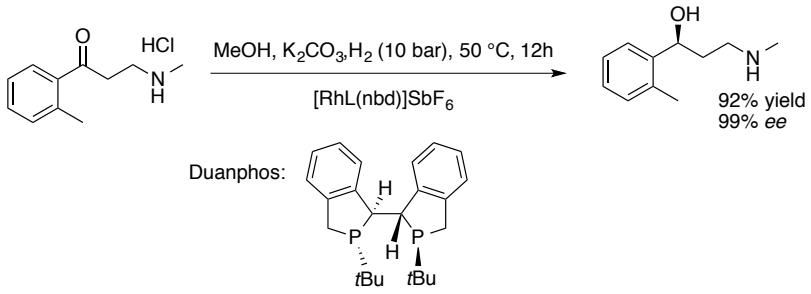
Alternatively, the reduction of β-amino ketones with $LiAlH_4$ provides another interesting synthetic pathway (Scheme 2.2).[14-17]



Scheme 2.2 Diastereoselective synthesis of γ-amino alcohols through the reduction of β-amino ketones.

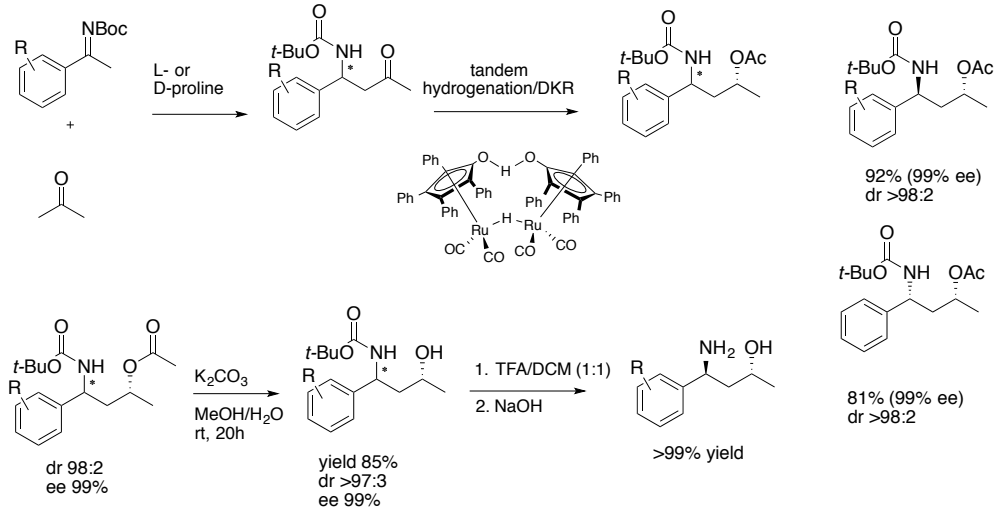
As far as the enantioselective synthesis of γ-amino alcohols is concerned, it is worthy to mention that Zhang et al.,[18] have described the hydrogenation of a series of β-secondary-amino ketone hydrochlorides with remarkably high

enantioselectivity in the presence of a Rh complex containing a highly electro donating P-chiral bisphospholane ligand (Scheme 2.3).



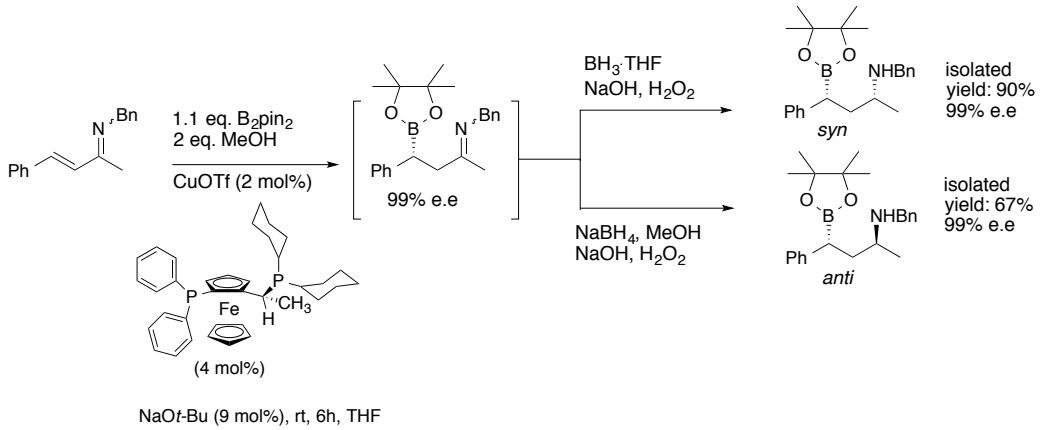
Scheme 2.3 Enantioselective hydrogenation of β-secondary-amino ketones with Rh complexes.

Another interesting methodology to prepare enantioenriched *syn*- and *anti*-γ-amino alcohols *via* β-amino ketones, involved a subsequent reduction/dynamic kinetic asymmetric transformation, which efficiently combines organo-, organometallic and enzymatic catalysis (Scheme 2.4).[19]



Scheme 2.4 Efficient two-step procedure combining organo-, organometallic and enzymatic catalysis.

Fernández and Whiting's groups also contributed to the enantioselective synthesis of enantioenriched *syn*- and *anti*-1,3-amino alcohols, *via* a model of efficient chirality transfer in the one pot Cu-catalyzed β-boration of α,β-unsaturated imines/reduction/oxidation sequence (Scheme 2.5).[20,21]



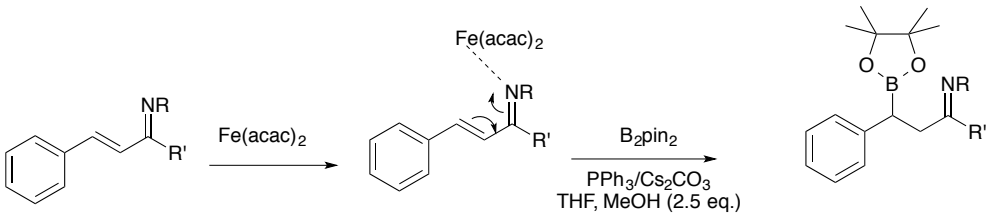
Scheme 2.5 One pot β-boration/reduction/oxidation sequence.

2.2 Work hypothesis.

In the present chapter we describe the attempts to carry out the β-boration of α,β-unsaturated imines in a transition metal-free context, to validate a new approach towards the enantioselective synthesis of γ-amino alcohols in a more friendly environmental media.

Our hypothesis of work is to preactivate the substrate with a chiral transition metal-free adduct, such as chiral phosphines.

An early experiment carried out in our group to perform the β-boration of (E)-1-phenyl-N-(4-phenylbutan-2-ylidene)-methanamine in absence of Cu(I) salt as precatalyst required the substrate preactivation by a Lewis acid such as Fe(II) and Fe(III) salts (Scheme 2.6).[22]

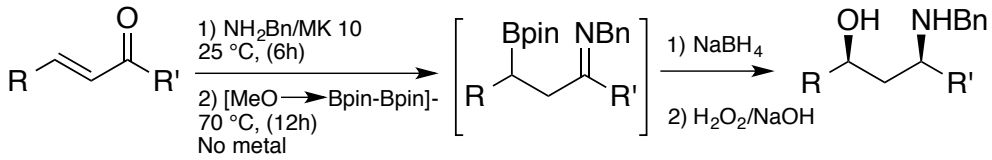


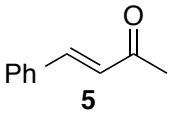
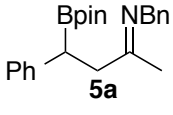
Scheme 2.6 Iron mediated β-boration reaction of α,β-unsaturated imines.

2.3 Results and discussions.

A model α,β-unsaturated imine, (E)-1-phenyl-N-(4-phenylbutan-2-ylidene)-methanamine, was generated *in situ* from 4-phenyl-3-buten-2-one (**5**) and benzylamine in THF with the dehydrating agent, Montmorillonite MK-10 (Table 2.1, entry 1). After 6 hours, the boron reagent bis(pinacolato)diboron was added to the intermediate α,β-unsaturated imine and the reaction was heated up to 70 °C.

Table 2.1 *In situ* α,β-unsaturated imines formation followed by organocatalytic β-boration with B_2pin_2 [a]



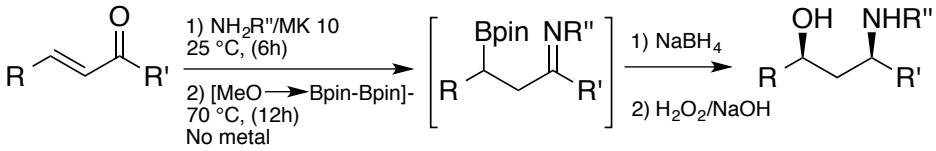
Entry	Substrate	Additive	Product	% Conv [IY][c]
1	 **5**	–	 **5a**	–
2	"	Cs_2CO_3/ MeOH	"	–
3	"	PCy_3/ Cs_2CO_3/ MeOH	"	99 [56]
4	"	PCy_3	"	–

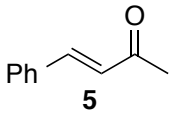
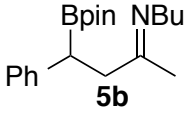
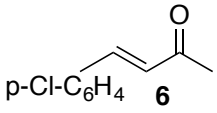
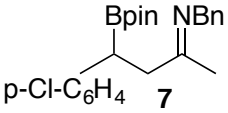
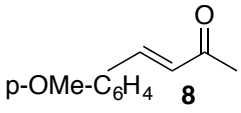
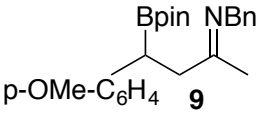
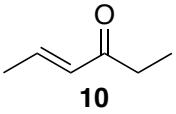
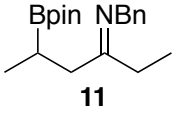
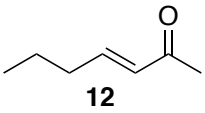
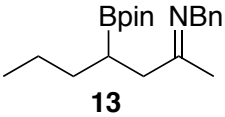
[a] Standard conditions: ketone (0.5 mmol), NH_2Bn (0.5 mmol), THF (2 mL), MK-10 (140 mg), B_2pin_2 (1.1 eq), Cs_2CO_3 (15 mol%), MeOH (2.5 eq), PCy_3 (10 mol%). [b] Conversion determined by ^1H NMR spectroscopy. [c] Isolated yield calculated for *syn*-γ-amino alcohol.

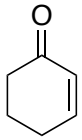
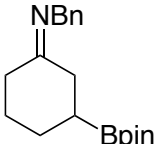
The desired borylated product **5a** was not observed (Table 2.1, entry1) and also the addition of MeOH and an inorganic base to activate the diboron reagent *via* quaternization was insufficient to give the expected product (Table 2.1, entry 2). Only when a catalytic amount of the phosphine PCy_3 (10 mol%) was added, the reaction could smoothly proceed to the product formation (Table 2.1, entry 3). However, the replacement of the base by the phosphine was not able to affect the conversion positively (Table 2.1, entry 4). It seemed that the combination of MeOH/base was necessary to activate the diboron reagent and that the role of the phosphine was to preactivate the substrate as it has been already showed in the analogue metal-free β-boration of α,β-unsaturated carbonyl compound, which were also assisted by phosphines.[23] The isolated yields were obtained by transformation of the β-borated imines into the corresponding γ-amino alcohols through one-pot reduction/oxidation.

Following these preliminary results, the study was extended to other α,β-unsaturated imines generating a wide range of β-borated imines. Interestingly, *n*$BuNH_2$ was also a suitable amine for the imine formation with **5** and also compatible with the organocatalytic protocol to afford the product **5b**, quantitatively (Table 2.2, entry 1). The reaction demonstrated to be quite general and substitution at the *para* position of aromatic rings of the ketone substrates **6** and **8** did not change the reaction outcome (Table 2.2, entry 2 and 3). Also α,β-unsaturated ketones with an alkyl chain at the β position and cyclic enones could be efficiently transformed into the corresponding β-borated imine (Table 2.2, entry 4-6).

Table 2.2 *In situ* α,β-unsaturated imines formation followed by organocatalytic β-boration with B_2pin_2 and reduction. [a]

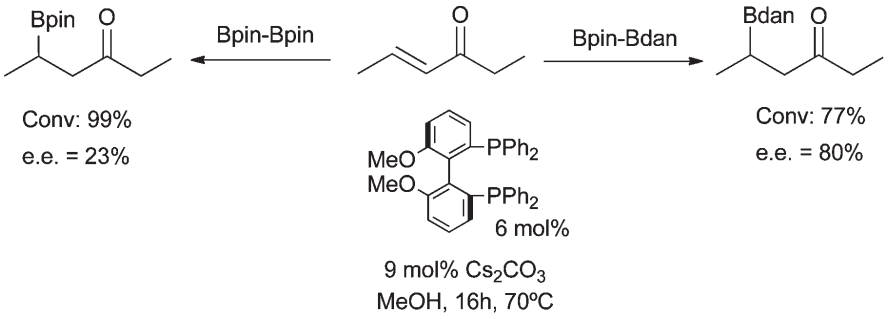


Entry	Substrate	Additive	Product	% Conv.[b] [IY][c]
1[d]	 **5**	PCy_3/ Cs_2CO_3/ MeOH	 **5b**	90 [66]
2	 **6**	PCy_3/ Cs_2CO_3/ MeOH	 **7**	99 [47]
3	 **8**	PCy_3/ Cs_2CO_3/ MeOH	 **9**	96 [37]
4	 **10**	PCy_3/ Cs_2CO_3/ MeOH	 **11**	95 [51]
5	 **12**	PCy_3/ Cs_2CO_3/ MeOH	 **13**	99 [68]

6	 **14**	PCy_3/ Cs_2CO_3/ MeOH	 **15**	97 [30]

[a] Standard conditions: ketone (0.5 mmol), NH_2Bn (0.5 mmol), THF (2 mL), MK-10 (140 mg), B_2pin_2 (1.1 eq), Cs_2CO_3 (15 mol%), MeOH (2.5 eq), PCy_3 (10 mol%). [b] Conversion determined by ^1H NMR spectroscopy. [c] Isolated yield calculated for *syn*-γ-amino alcohol, [d] NH_2Bu (0.5 mmol).

Once the synthesis of β-borated imines was achieved, the asymmetric version of the same reaction was considered to study next. It was thought that by substituting PCy_3 with a chiral phosphine, the latter could interact with the substrate and generate a chiral environment for the β-boration with the Lewis adduct [i.e MeO^- → Bpin–Bpin]. This concept has already been successfully demonstrated in the β-boration of α,β-unsaturated ketones with B_2pin_2[24] or BpinBdan (dan = 1,8-diaminonaphthalene) (Scheme 2.7), and the hypothesis of the role of the phosphine in the asymmetric induction has also been postulated from both an experimental and theoretical point of view.[25]



Scheme 2.7 β-Boration of α,β-unsaturated ketones with B_2pin_2 and BpinBdan (dan = 1,8-diaminonaphthalene), assisted by chiral phosphines.

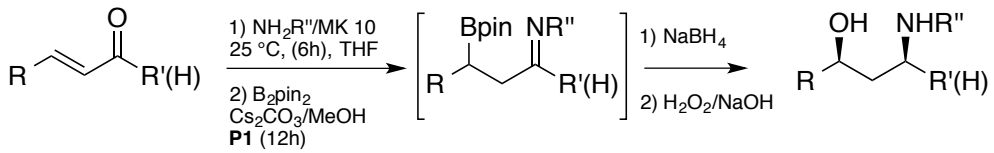
The addition of chiral phosphines to the borylation of tosylaldimines has also been proved to be beneficial to the formation of 1,2-amino alcohols.[26]

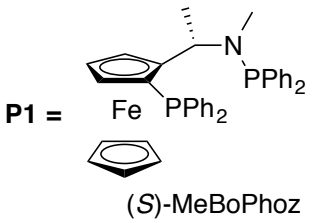
However, since imine functionality is more sterically hindered and less polarized than the carbonyl group, we were interested to ascertain whether asymmetric induction would be more or less efficient. Hence, we started our studies from substrate **5** and conducted the imine formation with benzylamine, followed by β-boration with the Lewis acid-base [MeO^- → Bpin–Bpin] adduct in the presence of a series of chiral diphosphines. Preliminary results using chiral Josiphos-type of diphosphines did not provide any significant asymmetric induction, which contrasts with the efficient trends observed with the corresponding ketones.

Remarkably, when the [MeO^- → Bpin–Bpin] adduct was used with the diphosphine (**P1**), total conversion was observed together with moderate enantioselectivity of the β-borated product (54% *ee*, Table 2.3, entry 1). When subtle changes were made to the reaction conditions, such as a lower base loading or a different reaction temperature, conversions and enantio- selectivities remained essentially unchanged. However, when the β-boration was carried out in the presence of CuCl (3 mol%), conversions from **5** to **5a** were higher but enantioselectivities were lower (32% *ee*, Table 2.3, entry 2). Note that the isolated yields of the product are given for the final *syn*-γ-aminoalcohol after a highly stereoselective reduction protocol with $NaBH_4$ in MeOH, followed by oxidation with H_2O_2 in NaOH.

Extending this study to other α,β-unsaturated imines, the formation of β-borated compounds **7**, **9**, **11** and **16**, resulted in a moderate asymmetric induction, that was higher than the analogue with Cu(I) as precursor of catalyst, (Table 2.3, entries 5-12).

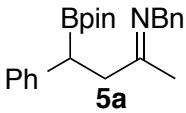
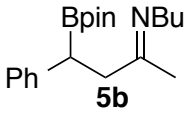
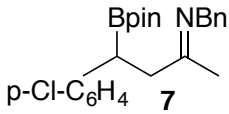
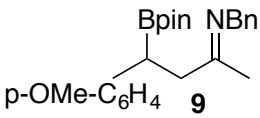
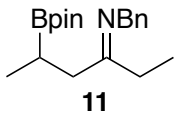
Table 2.3 Aymmetric organocatalytic versus asymmetric Cu(I) catalyzed β-boration of *in situ* formed α,β-unsaturated imines with (*S*)-MeBoPhoz, towards γ-amino alcohols [a]

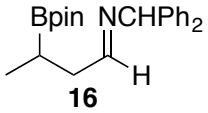




Method A: metal free, 70 °C

Method B: same as A but adding 3 mol% of CuCl, rt

Entry	β-Borated imine	Method	% Conv.[b]	% *ee*[c]	% I.Y.[d]
1	 **5a**	A	90	54	59
2		B	99	32	40
3	 **5b**	A	94	53	47
4		B	80	32	40
5	 **7**	A	98	50	49
6		B	95	45	43
7	 **9**	A	96	70	61
8		B	88	61	57
9	 **11**	A	99	51	48
10		B	92	33	57

11	 **16**	A	99	57[e]	73
12		B	95	29[e]	52

[a] Condition for method A: ketone or aldehyde (0.5 mmol), amine (0.5 mmol), THF (2mL), MK-10 (140 mg), B_2pin_2 (1.1 eq), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), (*S*)-MeBoPhoz (10 mol%), 70 °C; for method B: same as method A + CuCl (3 mol%), rt. [b]Conversion determined by ^{1}H NMR spectroscopy. [c]Enantioselectivity determined from HPLC-MS. [d] Isolated yield for the corresponding γ-amino alcohol. [e] *ee* calculated on the 4-(*N*-benzhydrylacetamido)butan-2-yl acetate derivative.

Since (*S*)-MeBoPhoz has been shown to be the most active and enantioselective additive for accessing β-boryl imines, in this metal-free context, we extended this study to other similar chiral phosphines, **P2–P4**. We concluded that (*R*)-PhEt-(*R*)-BoPhoz (**P4**) provides comparable asymmetric induction than the close phosphine **P1**, and higher than the enantioselectivities provided by the other analogues, **P2** and **P3**, in which the amine is either mono- or di-substituted (Fig. 2.2).

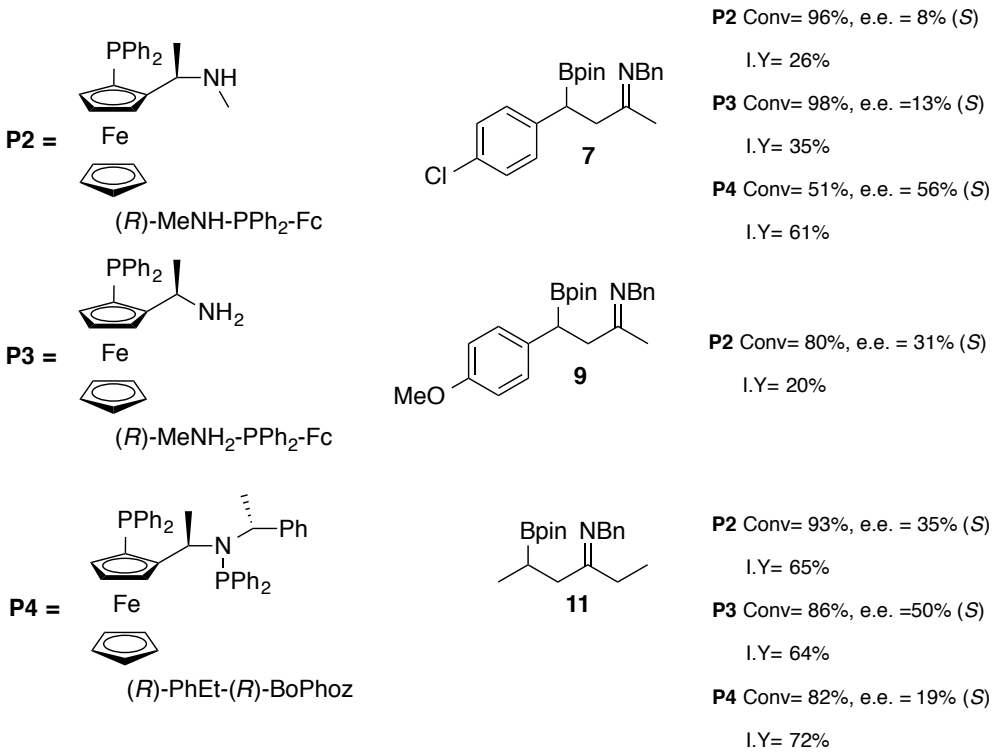
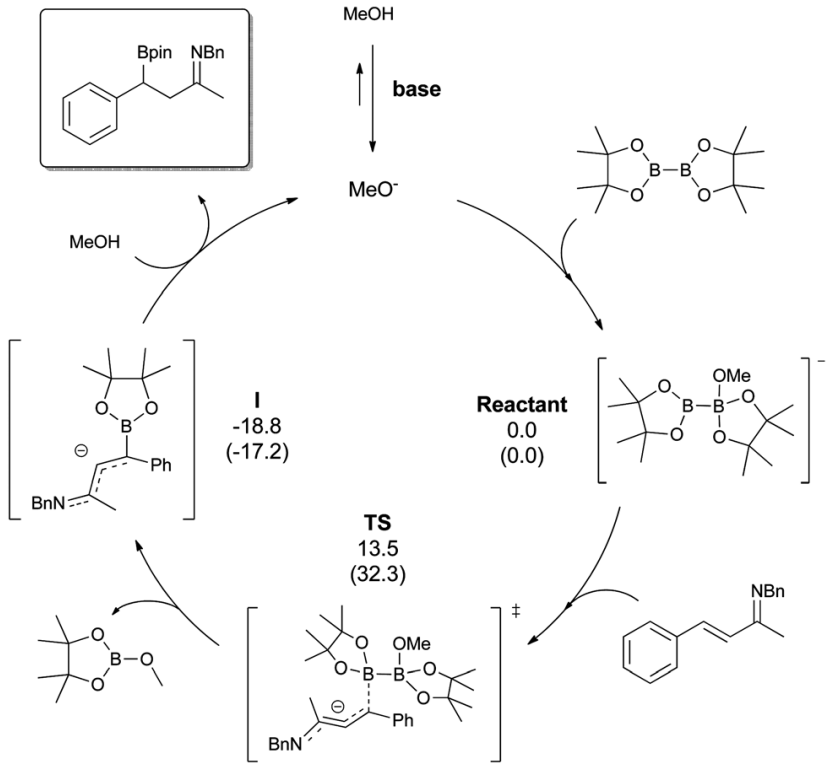


Fig. 2.2 Comparison of the chiral phosphine additives **P2-P4** for asymmetric β-boration of α,β-unsaturated imines **7, 9, 11**. I.Y data given as γ-amino alcohol.

To gain a deeper insight into the reaction mechanism and compare with other substrates that have been previously reported,[27] a member of the group, Dr. X. Sanz under the supervision of Dr. C. Bo, conducted DFT-based theoretical studies (Scheme 2.8).



Scheme 2.8 Mechanistic proposal on the organocatalytic β-boration of α,β-unsaturated imines. Electronic energies and Gibbs free energies (in parentheses) of the involved species in relation to the [MeO → Bpin–Bpin]$^-$ adduct are shown. All energies are in Kcal. mol^{-1}.

Initially, it has been postulated that the methoxide ion can quaternize a boronatom of the B_2pin_2 molecule forming the activated adduct [MeO → Bpin–Bpin]$^-$ (chosen as the origin of the energies). This adduct can then react with the model α,β-unsaturated imine through a transition state TS, which corresponds to the nucleophilic attack of the sp^2 boron atom on the β-carbon of the α,β-unsaturated imine.

Dr. X. Sanz and Dr. C. Bo reported that the structural features of the TS show the cleavage of the B–B bond ($\Delta d_{B\text{-}B}$ = 0.257 Å) and the formation of the new B–C bond ($d_{B\text{-}C}$ = 2.078 Å). After this transition state (TS), a negatively charged intermediate I is formed. Also in this step, a molecule of (pin)B-OMe is released as the by-product. The anionic intermediate I is then protonated in the presence of an excess of B_2pin_2 and MeOH, regenerating again the active species [MeO → Bpin–Bpin]$^-$ and hence the β-borated product. At this point, they compared energy values computed herein, with those obtained for the metal-free β-boration of ketones, esters and aldehydes.[27] For the model imine (E)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine, (**5a**), the transition state TS is higher ($\Delta G^{\neq}$ = 32.3 kcal mol^{-1}) than that found for acrolein ($\Delta G^{\neq}$ = 16.7 kcal mol^{-1}), 3-buten-2-one ($\Delta G^{\neq}$ = 18.7 kcal mol^{-1}), methyl acrylate ($\Delta G^{\neq}$ = 21.5 kcal mol^{-1}) and styrene ($\Delta G^{\neq}$ = 25.1 kcal mol^{-1}), but lower in energy than propylene ($\Delta G^{\neq}$= 35.9 kcal mol^{-1}). This fact can be explained by the lower electrophilicity of the C_β of the α,β-unsaturated imine, compared with other activated olefins, which makes it less reactive towards the nucleophilic attack. Moreover, the intermediate I for the imine (ΔG = –17.2 kcal mol^{-1}) is energetically more stable than the reactants, but less stable than the corresponding analogues for the activated alkenes.[27] This can be also rationalized by the fact that the negative charge that is generated is more stabilized by the oxygen atom than the nitrogen due to their different electronegative characters. It is worth mentioning that the reaction energies computed by Dr. X. Sanz and Dr. C. Bo for this model α,β-unsaturated imine substrate are in a similar range to those previously computed for ketones, aldehydes and esters, thus justifying the similarity in the reaction conditions (T = 70 °C) as described above.

Finally, they addressed the role of the chiral phosphine in not only mediating the catalytic reaction but importantly, guiding the asymmetric C–B bond formation. A possible interaction between a model phosphine of reduced steric congestion, PMe_3, and the α,β-unsaturated imine **5a**, is to form a phosphonium enolate intermediate (Fig. 2.3).[28-30]

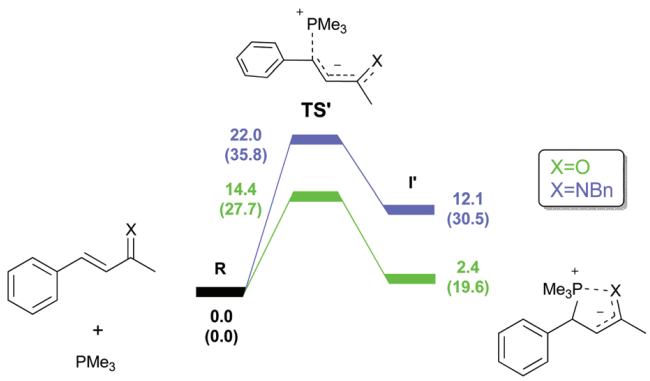
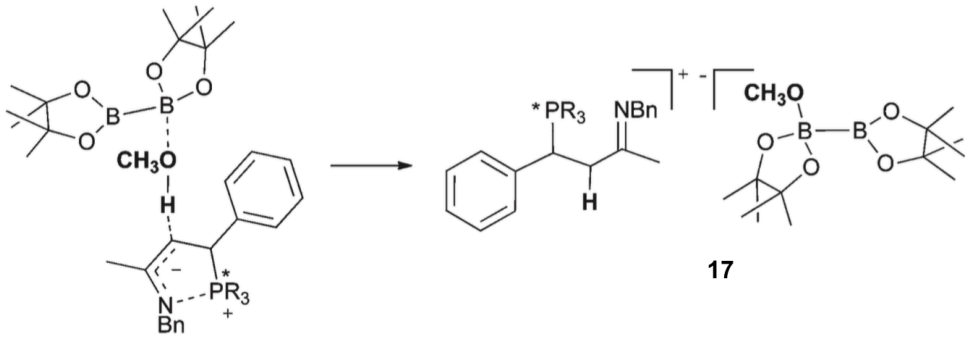


Fig. 2.3 Reaction energy profile for the formation of phosphonium eno- lates. Electronic and Gibbs free energies calculated by Dr. X. Sanz and Dr. C. Bo (in parentheses) are given in kcal. mol^{-1}

They compare this with the corresponding α,β-unsaturated ketone-derived enolate species (Fig. 2.3). Interestingly, the imine-derived phosphonium enamide formed from PMe_3 and **5a** is higher in energy than the corresponding ketone-derived phosphonium enolate intermediate, which explains why that reaction has to be carried out at 70 °C, and does not proceed readily at lower temperature. Hence, the origin of the asymmetric induction when using (*S*)-MeBoPhoz may result from the protonation of the zwitterionic phosphonium enamide with MeOH, and formation of a tight ion-pair between the resulting $[B_2pin_2{\cdot}MeO]^-$ adduct and the chiral phosphonium imine, as in **17** (Scheme 2.9).



Scheme 2.9 Suggested formation of the ion pair.

2.4 Conclusions

In this chapter, the first example of transition metal-free β-boration of *"in situ"* formed α,β-unsaturated imines was developed, highlighting the compatibility of the organocatalytic Bpin addition with the imine formation in the presence of both ketone and amine. The reaction shows little dependence upon substrate electronics and shows consistently high conversion. Importantly, the use of chiral phosphines, such as the diphosphine (*S*)-MeBoPhoz, enables the catalytic asymmetric version to be realized with moderate asymmetric induction. Interestingly, the enantioselectivity is higher than that induced by the same chiral phosphines when modified using the corresponding Cu(I)-based catalytic system. The mechanism of the organocatalytic β-boration of these α,β-unsaturated imines has been postulated from a theoretical point of view, and seems to involve quaternization of the diboron reagent with methoxide while the role of the phosphine has been regarded to the ion pair formation.

2.5 Experimental part.

2.5.1 Instrumentation and chemical

All reactions and manipulations were carried out under Ar using Schlenk-type techniques or Radleys Carousel 12 reactions. Dry solvents were dried using a MBRAUN Solvent Purification System (MB-SPS). Bis(pinacolato)diboron was used as purchased from AllyChem. Phosphines were supplied by Johnson Matthey or Solvias and used without further purifications. Benzylamine and *n*-butylamine were distilled over KOH pellets and CaH_2 respectively. Molecular sieve (3 Å, 1-2 mm) beads were supplied by Alfa Aesar and stored at 100 °C prior to use, followed by cooling under Ar. Montmorillonite K 10 was provided by Sigma Aldrich and stored at 100 °C prior to use, followed by cooling under Ar. All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise.

High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector or a Hewlett-Packard HP 5989 MS at an ionizing voltage of 70 eV. Chiral HPLC was carried out on either a Chiralpak AD-H column (dimensions 250 × 4.6 mm) or Chiralpak OD-H column (dimensions 250 x 4.6 mm) in order to determine enantiomeric excesses (ees). Alternatively ESI-TOF was also used. NMR spectra were obtained using a Varian Mercury 400 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane, referenced to the chemical shift of residual solvent resonances. Coupling constants (J) are given in Hz and NMR peaks are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements.

2.5.2 General experimental procedure for organocatalytic β-boration of α,β-unsaturated ketimines generated *in situ* using bis(pinacolato)diboron.

Montmorillonite K 10 (140 mg) and ketone or aldehyde (0.5 mmol) were added under Ar into an oven-dried Schlenk tube with a stirring bar. THF (2 mL) and amine (0.5 mmol) were added and the resulting mixture was stirred for 6 h at rt. After addition of phosphine (10 mol%), Cs_2CO_3 (15 mol%), bis(pinacolato)diboron (1.1 eq), MeOH (2.5 eq), the reaction mixture was stirred overnight at 70 °C. The conversion and the enantiomeric excess (ee) were determined by NMR spectroscopy and HPLC-UV, respectively.

2.5.3 General experimental procedure for organocatalytic β-boration of α,β-unsaturated aldimines generated *in situ* with bis(pinacolato)diboron.

Molecular sieves 3Å (1g), aldehyde (1 mmol), THF (4 mL) were added under Ar to an oven-dried Schlenk tube with a stirring bar. Benzhydrylamine (1 mmol) was added and the resulting mixture stirred for 5 h at r.t.

In another oven-dried Schlenk tube, phosphine (6 mol%), NaO*t*-Bu (9 mol%), bis(pinacolato)diboron (1.1 eq) were added under Ar. The above aldimine solution was decanted to the latter vessel, and the combined mixture was stirred at rt. After 5 mins, MeOH (1.25 mmol) was added and the reaction mixture was heated at 70 °C overnight.

2.5.4 General procedure for the synthesis of γ-amino alcohols.

A solution of $NaBH_4$ (1.5 mmol) in methanol (2 mL) was added to a solution of the β-borated ketimine/aldimine in THF and the mixture stirred for 3 h at rt. All solvent was removed under reduced pressure, and the mixture was redissolved in THF (4 mL), followed by the addition of aqueous NaOH (0.6 mL, 20% w/v solution), H_2O_2 (0.25 mL, 30% w/v solution). The resulting mixture was refluxed for 1 h, cooled to rt, and the mixture was partionated between EtOAc and saturated aqueous NaCl solution. The aqueous layer was re-extracted further with EtOAc (3 x). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield a crude yellow oil. Purification was achieved by silica gel chromatography using a mixture of petroleum ether and EtOAc.

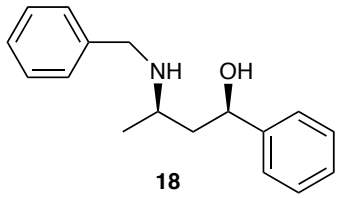
2.5.5 Synthesis of γ-amino alcohols O,N-diacetate derivatives.

When aldehydes were used as substrates for the synthesis of γ-aminoalcohols, transformation into diacetate was required in order to determine the enantioselectivity.

The γ-amino alcohol (0.19 mmol), pyridine (0.5 mL, 6.2 mmol) and acetic anhydride (0.5 mL, 5.3 mmol) were combined in DCM (3.0 mL) and stirred overnight. The resulting solution was diluted with DCM (10.0 mL), washed with HCl (3 x 10 mL, w/v 20%) and water (3 x), and the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to yield a dark yellow oil.

2.5.6 Characterization of γ-amino alcohols:

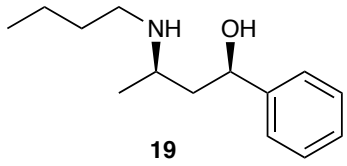
3-(Benzylamino)-1-phenylbutan-1-ol



18

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33- 7.13 (m, 10H), 4.84 (dd, *J* 10.6, 2.0 Hz, 1H), 3.92 (d, *J* 12.5 Hz, 1H), 3.71 (d, *J* 12.5, 1H), 3.09 - 2.95 (m, 1H), 1.68 (dt, *J* 14.4, 2.3 Hz, 1H), 1.52 (dt, *J* 14.4, 10.8 Hz, 1H), 1.14 (d, *J* 6.3 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 145.3, 139.3, 128.6, 128.4, 128.2, 1271.3, 127.0, 125.6, 75.4, 54.3, 50.9, 46.1, 21.1

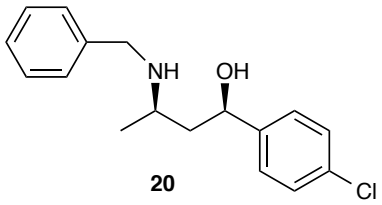
3-(Butylamino)-1-phenylbutan-1-ol



19

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 5H), 4.95 (dd, *J* 11.2, 2 Hz, 1H), 3.07-3.02 (m, 1H), 2.86-2.82 (m, 1H), 2.59-2.55 (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 NMR** (100.6 MHz, $CDCl_3$) δ 142.3, 128.4, 127.5, 125.7, 74.1, 55.2, 50.9, 44.4, 30.6, 20.7, 20.0, 14.0

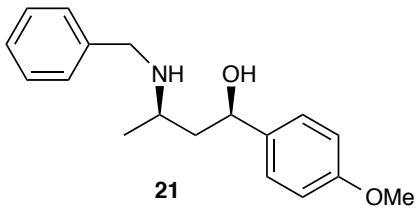
3-(Benzylamino)-1-(4-chlorophenyl)butan-1-ol



20

^{1}H NMR (400 MHz, $CDCl_3$) 7.37 – 7.25 (m, 5H), 7.20 (d, *J* 8.4, 2H), 7.13 (d, *J* 8.4 Hz, 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), 3.10-3.20 (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 NMR** (100.6 MHz, $CDCl_3$) 139.7, 138.4, 133.4, 131.6, 128.8, 127.9, 127.5, 116.8, 63.4, 55.2, 46.1, 27.4, 20.6

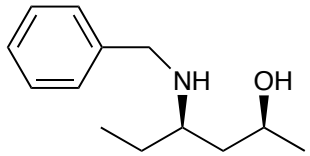
3-(Benzylamino)-1-(4-methoxyphenyl)butan-1-ol



21

^{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, 2.0 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 NMR** (100.6 MHz, $CDCl_3$) δ 157.8, 136.2, 135.0, 130.2, 129.3, 128.6, 126.8, 113.8, 75.7, 57.0, 55.2, 54.6, 40.9, 19.2.

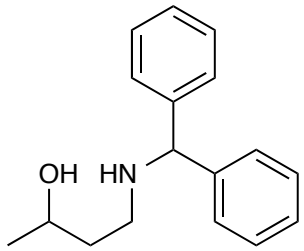
4-(Benzylamino)hexan-2-ol



22

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.05 (m, 1H), 3.85 (d, J 12 Hz, 1H), 3.63 (d, J 12 Hz, 1H), 2.70-2.80 (m, 1H), 1.70-1.30 (m, 4H), 1.10 (d, J 6.8Hz, 3H); 0.89 (t, J 7.2 Hz 7.2, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 139.4, 128.5, 128.5, 127.2, 69.2, 59.4, 50.2, 41.1, 26.3, 23.9, 9.4

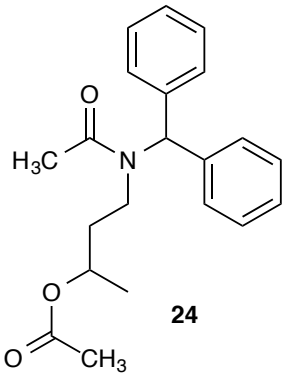
4-(Benzhydrylamino)butan-2-ol



23

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.17 (m, 10H), 4.78 (s, 1H), 4.02-3.94 (m, 1H), 2.95 (ddd, *J* 11.9, 3.6, 1.4 Hz, 1H), 2.71 (dt, *J* 10.6, 3.4 Hz, 1H), 1.69-1.47 (m, 2H), 1.17 (d, *J* 6.2 Hz, 1H). **^{13}C NMR**: (100.6 MHz, $CDCl_3$) δ 143.3, 142.8, 128.6, 128.6, 128.4, 127.2, 127.1, 126.9, 69.5, 67.9, 47.1, 37.5, 23.4.

4-(N-Benzhydrylacetamido)butan-2-yl acetate



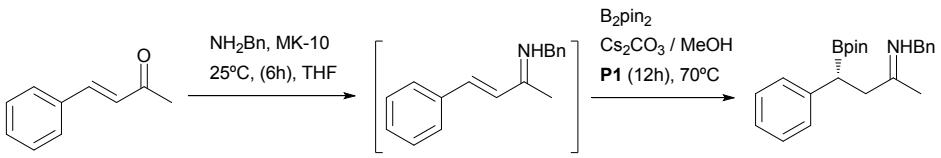
24

^{1}H NMR (400 MHz, $CDCl_3$) observed as a mixture of rotamers, major rotamer: δ 7.32-7.04 (m, 10H), 6.15 (s, 1H), 4.53-4.41 (m, 1H), 3.36-3.15 (m, 2H), 2.10 (s, 3H), 1.83 (s, 3H), 1.21-1.10 (m, 2H), 0.85 (t, *J* 6.4 Hz, 3H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.7, 170.4, 139.6, 139.1, 129.2, 129.1, 128.7, 128.7, 128.5, 128.0, 69.2, 66.0, 56.9, 41.4, 33.9, 21.7, 21.3.

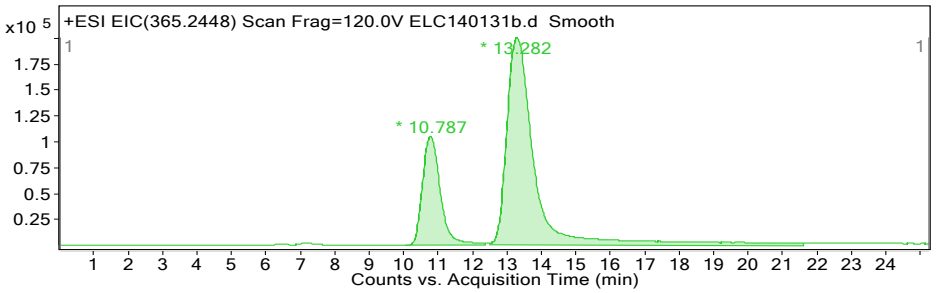
2.5.7 Analysis of the enantiomeric excesses (ees) by HPLC

Analysis of 1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2- ylidene)methanamine

The enantiomeric excess (ee) was obtained by chiral HPLC-MS analysis using a OD-H column (heptane:2-propanol, 99:1, flow rate 1mL/min, 25 °C). The evaluation was carried using an aliquot of β-borated imine.



54% ee in the presence of 10 mol% (*S*)-MeBoPhoz (**P1**)

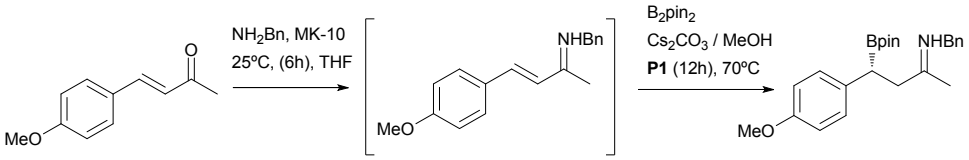


t_r (*S*)-enantiomer: 10.77 min,

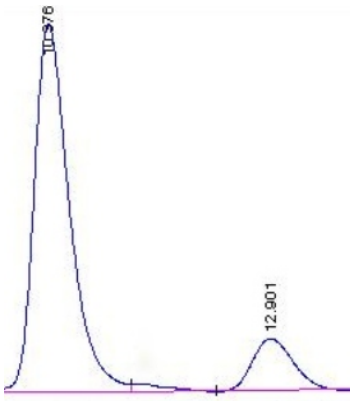
t_r (*R*)-enantiomer: 13.28 min

Analysis of N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)butan-2-ylidene)-1-phenylmethanamine

The ee was obtained by HPLC-UV analysis using a OD-H column (hexane:2-propanol, 98:2, flow rate 1mL/min, 25 °C). The wavelength used for the analysis was 210 nm. The evaluation was carried using an aliquot of β-borated imine.



70 % ee in the presence of 10 mol% (*S*)-MeBoPhoz (**P1**)

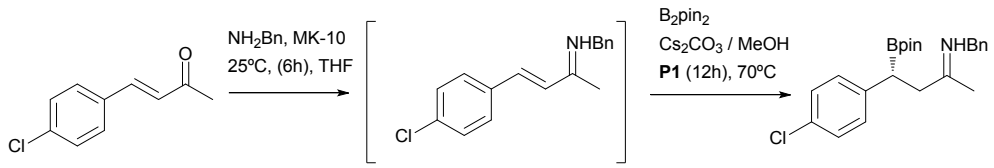


t_r (*S*)-enantiomer 12.90 min

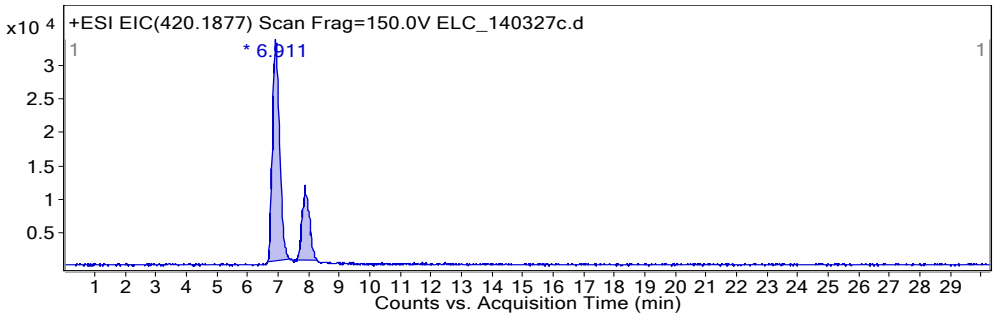
t_r (*R*)-enantiomer 10.37 min

Analysis of N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine

The enantiomeric excess was obtained by chiral HPLC-MS analysis using a OD-H column (hexane/2-propanol, 98:2, flow rate 1mL/min, 25 °C). The evaluation was carried using an aliquot of β-borated imine.



50 % ee in the presence of 10 mol% (*S*)-MeBoPhoz (**P1**)

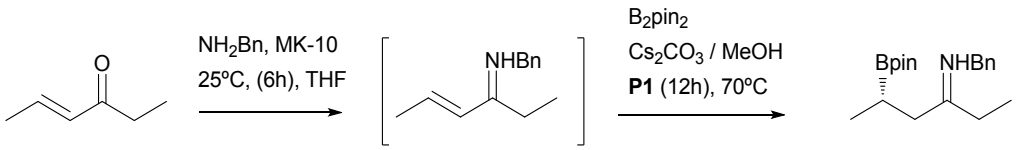


t_r (*R*)-enantiomer: 6.91 min

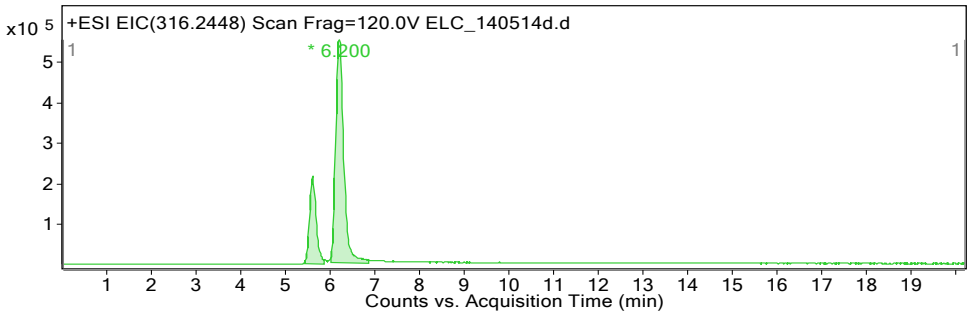
t_r (*S*)-enantiomer: 7.89 min

Analysis of 1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine

The ee was obtained by chiral HPLC-MS analysis using a OD-H column (hexane:2-propanol, 99:1, flow rate 1mL/min, 25 °C). The evaluation was carried using an aliquot of β-borated imine.

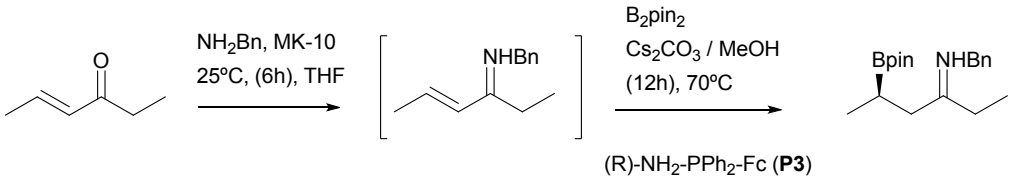


51% ee in the presence of 10 mol% (*S*)-MeBoPhoz (**P1**)

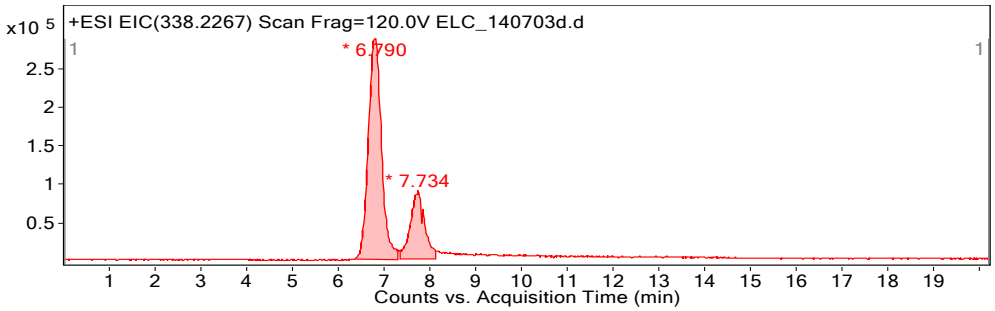


t_r (*S*)-enantiomer: 5.61min

t_r (*R*)-enantiomer: 6.20 min

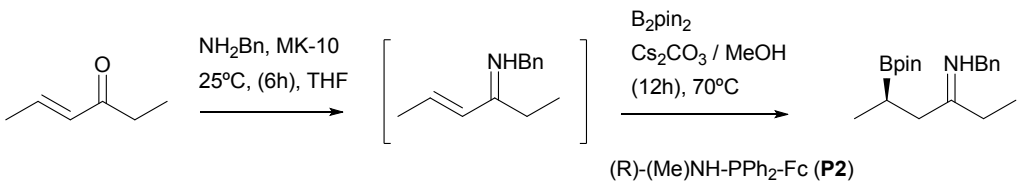


50% ee in the presence of 10 mol% (*R*)-NH_2-PPh_2-Fc (**P3**)



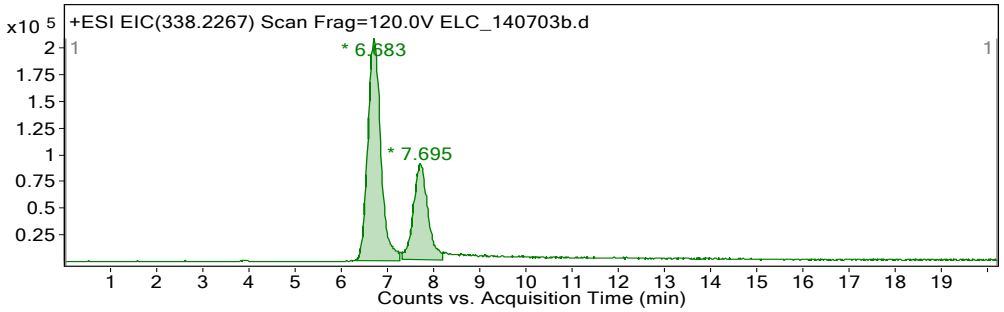
t_r (*S*)-enantiomer: 6.79min

t_r (*R*)-enantiomer: 7.73 min



(R)-(Me)NH-PPh$_2$-Fc (**P2**)

35% ee in the presence of 10 mol% (*R*)-MeNH-PPh$_2$-Fc (**P2**)

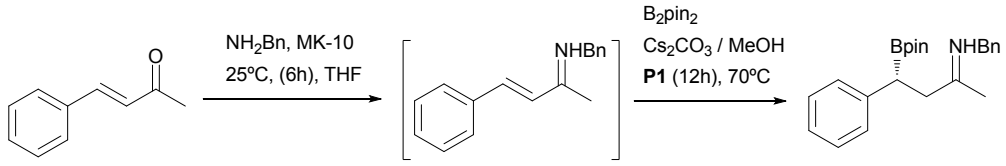


t_r (*S*)-enantiomer: 6.68min

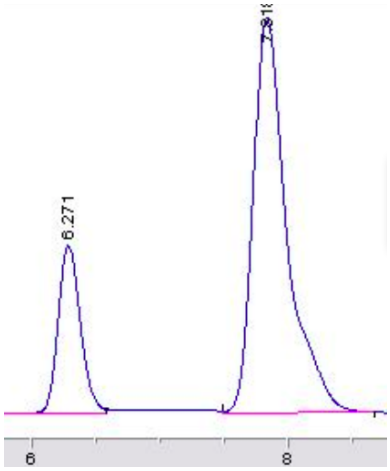
t_r (*R*)-enantiomer: 7.69 min

Analysis of *N*-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)butan-1-amine

The optimization of racemic mixture was obtained by chiral HPLC-MS analysis using a OD-H column (hexane:2-propanol, 98:2, fllowrate 1mL/min, 25 °C). The evaluation was carried using an aliquot of β-borated imine. In this particular case, the ee analysis was run by HPLC-UV (wavelength at 210 nm) using a ODH chiral column (hexane;2-propanol, 98:2, flow rate 1mL/min, 25 °C). The evaluation was carried out using an aliquot of β-borated imine.



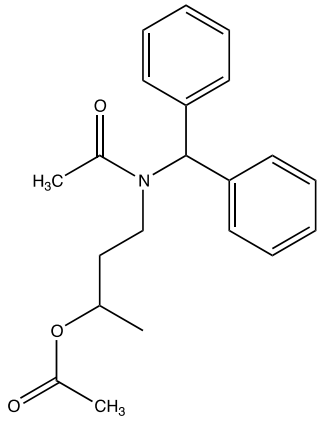
53 % ee in the presence of 10 mol% (*S*)-MeBoPhoz



t_r (*S*)-enantiomer: 6.27min

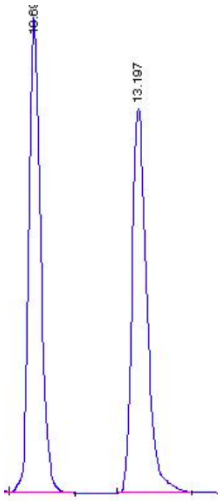
t_r (*R*)-enantiomer: 7.81 min

Anaylsis of 4-(*N*-benzhydrylacetamido)butan-2-yl acetate



The enantiomeric excess was obtained by HPLC-UV analysis using an AD-H column (hexane:2-propanol, 90:10, flow rate 1mL/min, 25 °C). The wavelength used for the analysis was 210 nm.

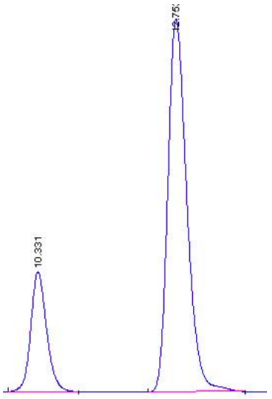
Racemic mixture with PCy_3



t_r (*S*)-enantiomer: 10.69 min

t_r (*R*)-enantiomer: 13.21 min

ee of 57% with (*S*)-MeBoPhoz



t_r (*S*)-enantiomer: 10.33 min

t_r (*R*)-enantiomer: 12.75 min

2.6 References.

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Chapter 3

β-Boration reaction towards the synthesis of bioactive compounds: Approaches to the total synthesis of Tramadol

3.1 Scope of the art on the synthesis of Tramadol.

In recent years, the Fernández's and Whiting's groups have jointly developed a new and efficient route towards the synthesis of γ-amino alcohols.[1] Inspired by the total synthesis of two bioactive compounds (Fluoxetine and Duloxetine) (Figure 3.1) reported by Whiting and co-workers,[2] it was decided to develop this methodology further with a more complex target, and apply a similar methodology for the synthesis of an important opioid pain killer called Tramadol (Figure 3.1).

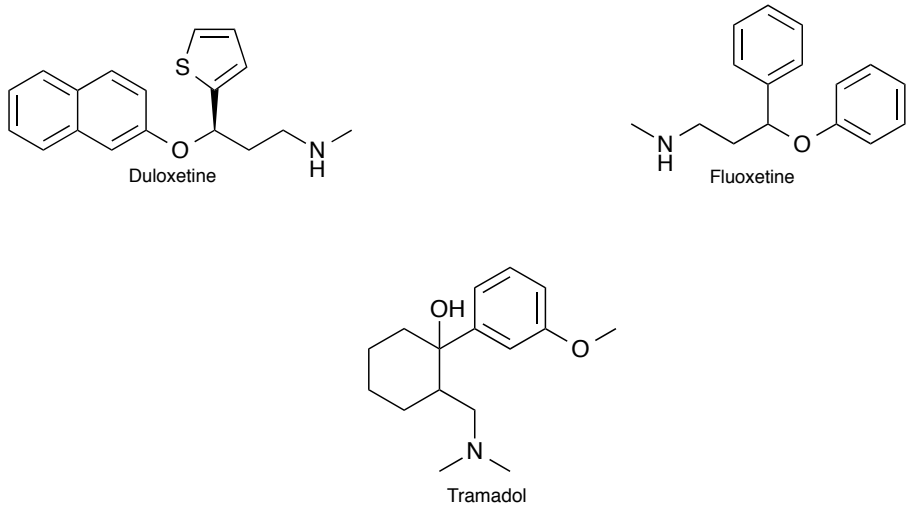
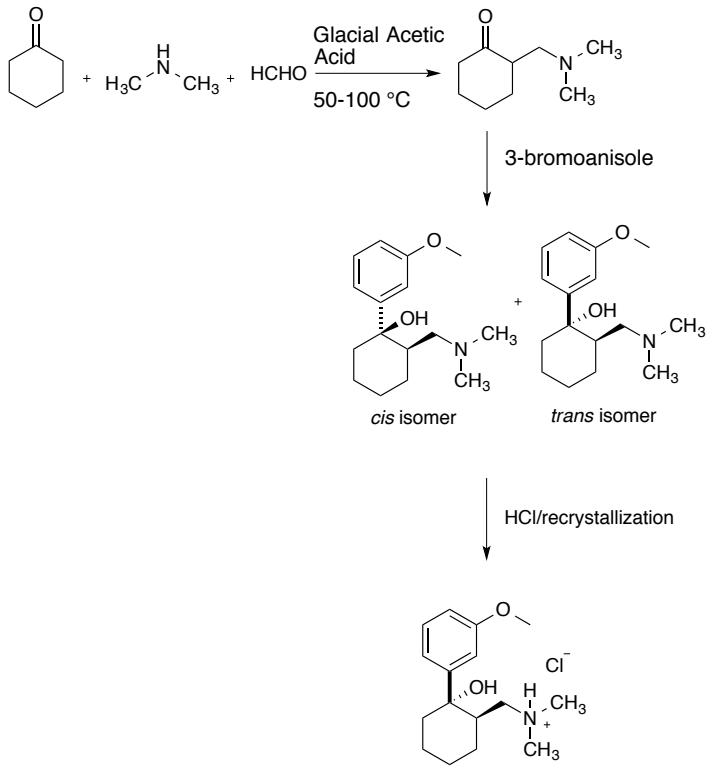


Fig 3.1. Structure of Duloxetine, Fluoxetine and Tramadol.

Tramadol is structurally related to codeine and morphine and it consists of two enantiomers, both of which contribute to analgesic activity *via* different

mechanisms. (+)-Tramadol and the metabolite (+)-*O*-Desmethyl-tramadol are agonists of μ-opiod receptors. (+)-Tramadol inhibits serotonin reuptake and (-)-Tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate.

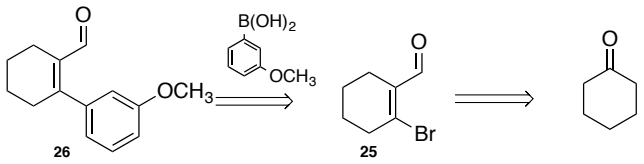
The synthesis of Tramadol as the hydrochloride salt has been reported in literature and consists of a Grignard reaction of 2-dimethylaminomethyl cyclohexanone with 3-bromoanisole.[3] The reaction provided, after purification through high *vacuum* distillation, a mixture of geometrical isomers (*cis* and *trans* in a 1:1 ratio) (Scheme 3.1). The mixture was then treated with HCl to afford, after recrystallization, the pharmacologically active *trans*-isomer.



Scheme 3.1 Conventional synthesis of Tramadol.

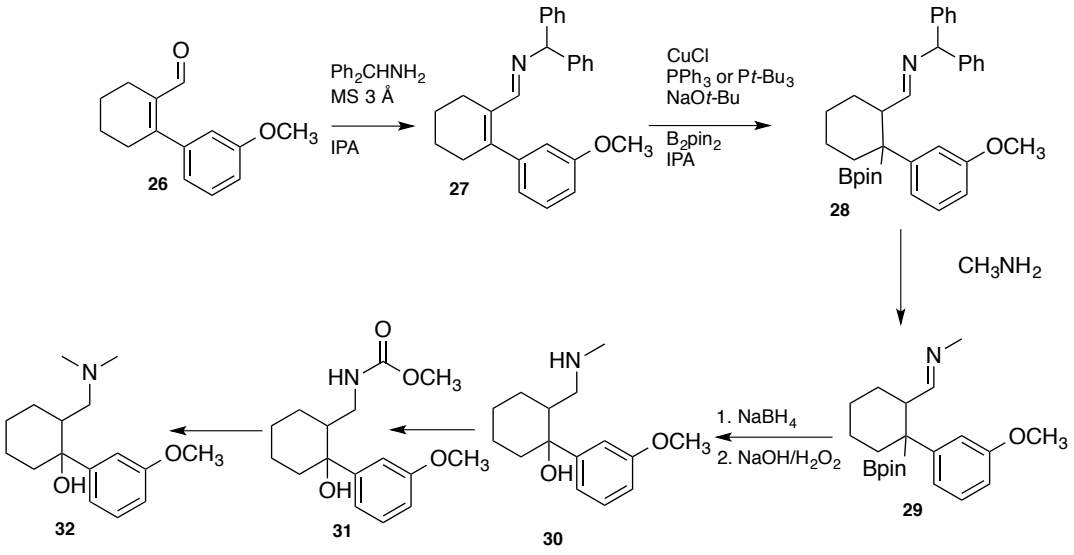
3.2. Work hypothesis.

As mentioned above, our group has extensively investigated the enantio- and diastereoselctive synthesis of γ-amino alcohols and since Tramadol belongs to this class of compounds, we tried to develop a new synthetic route. Towards this aim, the synthesis began with a suitable β-substituted α,β-unsaturated aldehyde **26** (Scheme 3.2).



Scheme 3.2. Retrosynthetic route to prepare **26**.

Once the starting material **26** (87% yield) was successfully synthesized, a pathway for the full synthesis was planned (Scheme 3.3).



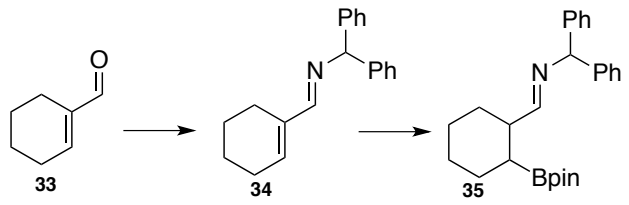
Scheme 3.3. Synthetic route of Tramadol through imine formation, β-boration, transimination, reduction and oxidation.

3.3 Results and discussion

The formation of imine **27** was monitored by ReactIR, which showed that it was complete after 3 hours. Then, the additives for the borylation of the imine **27** generated *in situ* were added in order to access the intermediate **28** (Scheme 3.3). However, the formation of species **28** was particularly difficult, with only a negligible conversion being observed. Hence, the next efforts were to try to understand why compound **27** was unreactive under such well established conditions.[4]

First of all, different ligands to modify Cu(I) salts were tested for the borylation of imine **27**. PPh_3 was not suitable for this reaction (zero conversion) and the even more nucleophilic P*t*-Bu_3 did not show any improvements in terms of conversion. Also, the use of the chiral ligand (*R*)-DM-Binap was used without any success. Next, different solvent systems were examined, including THF + 2.5 eq of MeOH, but no conversion was detected. Also in toluene, the β-boration did not occur and only **27** was detected by ^{1}H NMR. With this preliminary information about the reactivity of imine **27**, different approaches were considered.

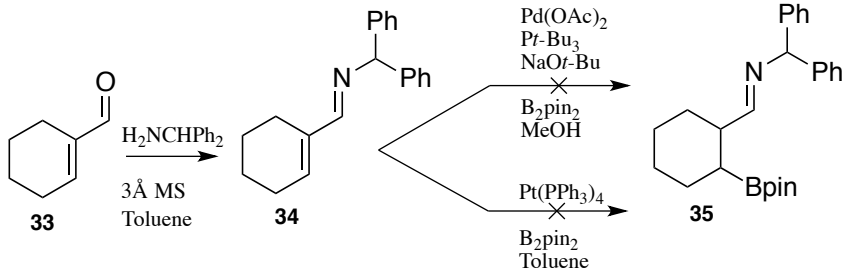
First of all, the same reaction conditions for the synthesis of **28** were reproduced using the commercially available cyclohex-1-enecarbaldehyde **33** (Scheme 3.4).
This attempt was carried out in order to optimize the β-borylation step, which is the crucial point of the total synthesis of Tramadol. Like in the case of **26**, the imine formation was completed within 3 hours affording **34** quantitatively. Therefore, the additives for the β-boration were added and the reaction was left stirring for further 16 hours. After this time the reaction was analysed by ^{1}H NMR, but only the intermediate **34** could be detected.



Scheme 3.4. Synthesis of the imine **34** and β-boration of the imine.

Since our group reported the organocatalytic borylation of α,β-unsaturated imines generated *in situ,*[5] another attempt was made to reproduce the same conditions in order to afford the imine **35** from intermediate imine **34**, which in turn was derived from starting aldehyde **33**. The mixture containing the preformed imine **34** (0.5 mmol) was treated with P*t*-Bu_3 (10 mol%), Cs_2CO_3 (15 mol%), B_2pin_2 (1.1 eq) and MeOH (2.5 eq) at 70 °C, but after 16 hours no conversion was noted and only **34** could be detected by ^{1}H NMR. This trial of organocatalytic conditions suggested that the presence of a more reactive metal catalyst was likely to be mandatory. For this reason different sources of metal catalysts systems were tested.

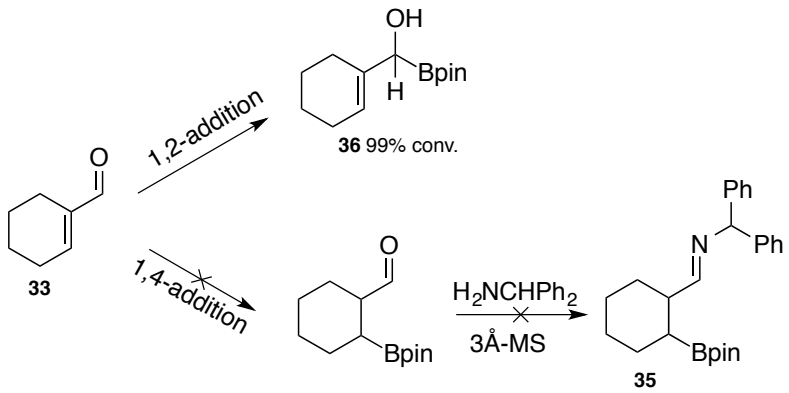
Fernández *et al.* reported in 2009 the first example of borylation of α,β-unsaturated esters catalyzed by Pd and Ni.[6] Hence, after the imine **34** formation, (0.5 mmol), $Pd(OAc)_2$ (5 mol%), P*t*-Bu_3 (10 mol%), Cs_2CO_3 (15 mol%), B_2pin_2 (1.1 eq) and MeOH (2.5 eq) were added, and the reaction was stirred for 16 hours at room temperature (Scheme 3.5).



Scheme 3.5. β-Boration attempts of **34** using $Pd(OAc)_2$ and $Pt(PPh)_4$ as catalytic system.

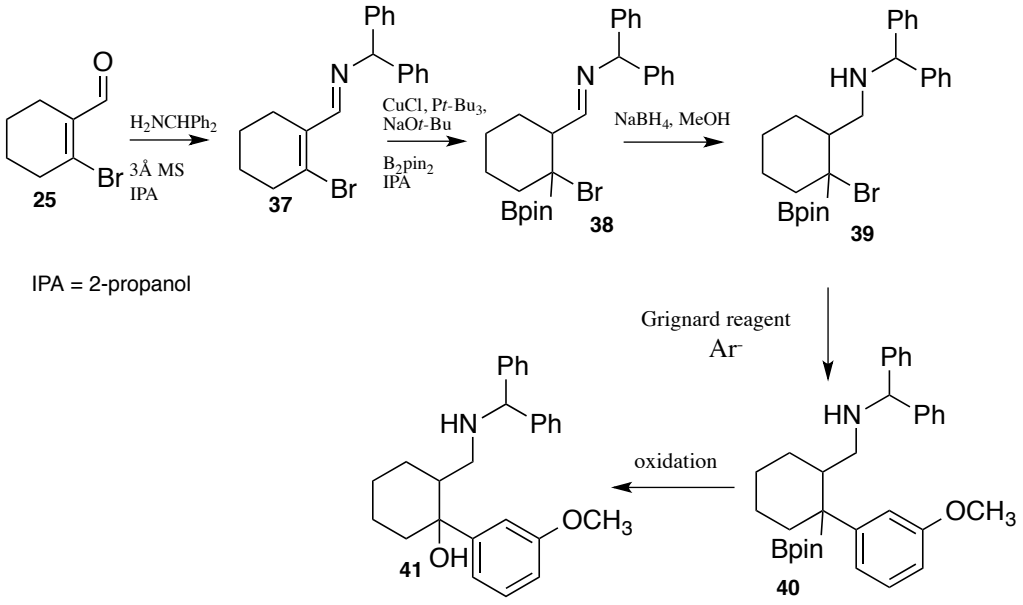
Unfortunately, no borylation to give **35** occurred and the α,β-unsaturated imine **34** was the only compound detected by ^1H NMR. In addition, $Pt(PPh_3)_4$ was tested as a plausible catalyst for the β-borylation and even in this case, no desired product was formed (Scheme 3.5).

The last attempt was to see if it was possible to selectively borylate (i.e. 1,4-addition), the starting material **33** and then to proceed with the condensation using benzhydrylamine to obtain the compound **35**. It is well-known that α,β-unsaturated aldehydes suffer from competitive 1,2-boryl addition and, therefore, this transformation was very challenging. In fact, the attempt of borylation of **33** did not work, providing only the undesired 1,2-addition product **36** quantitatively (Scheme 3.6).



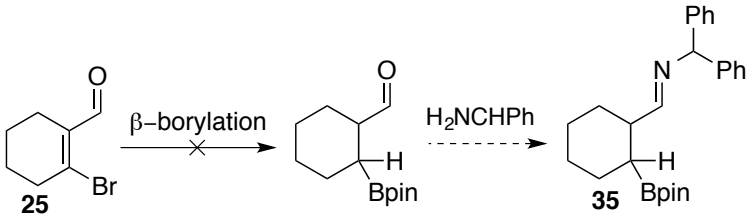
Scheme 3.6 Competition between 1,2- versus 1,4-addition of the Bpin moiety to the α,β-unsaturated aldehyde **33**.

Therefore, a new pathway for the synthesis of Tramadol was considered (Scheme 3.7).



Scheme 3.7 Alternative pathway of synthesis through β-boration of (*E*)-*N*-benzhydryl-1-(2-bromocyclohex-1-en-1-yl)methanimine (**37**).

2-Bromocyclohex-1-enecarbaldehyde **25**, prepared according to the literature[7] (I.Y. = 44%), reacted easily with benzhydrylamine to afford imine **37** in three hours (as determined by ^{1}H NMR). The next step consisted of the borylation of the imine **37** using the same conditions applied to the synthesis of **28** (see Scheme 3.3). The main idea of this pathway was to evaluate if it was possible to introduce the Bpin moiety and to isolate **39** after the one-pot imination-borylation-imine reduction of **25**. The purified intermediate **39** could then react with a suitable Grignard reagent or other orgamometallic species in a cross-coupling reaction to obtain the compound **40**, which would afford the tertiary alcohol **41** after oxidation of the C-B bond. However, during the synthesis, it was impossible to isolate the desired adduct **39.** Indeed, the β-boration of **37** was followed by ^{1}H NMR and after 16 hours only the α,β-unsaturated imine **37** could be detected in the reaction mixture. Therefore, as an alternative, the direct borylation of aldehyde **25** was considered as a plausible starting point (Scheme 3.8).

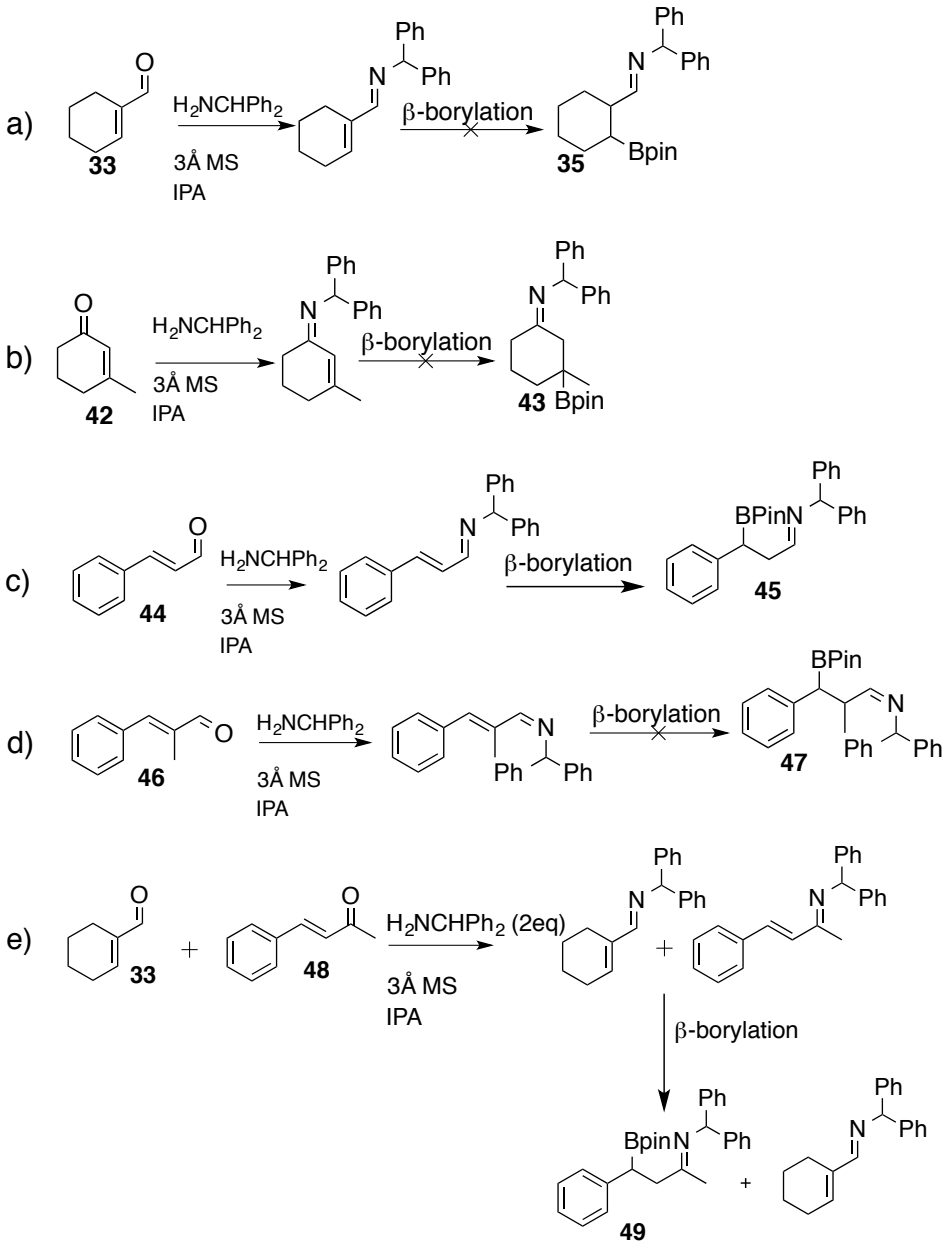


Scheme 3.8 Attempt to β-boration of α,β-unsaturated aldehyde **25**.

In fact, this aldehyde **25** should be more reactive than **33** because of the presence of an halogen which should make the β-position more electron deficient. However, the corresponding borylated product was not observed under the standard conditions and only the starting aldehyde **25** was identified as a product in the reaction mixture. Therefore, this pathway was also excluded.

In order to better understand why substrates **25**, **26** and **33** were totally inactive towards the formation of the corresponding borylated products, some comparative

and conformational studies were carried out, as outlined in composite Scheme 3.9.

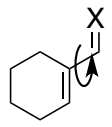


Scheme 3.9 Comparative studies between cyclic and acyclic structures.

As shown in Scheme 3.9, a series of different α,β-unsaturated compounds were examined using the same imination-borylation conditions as the reaction for the

synthesis of **28**. As previously reported in this chapter, the cyclic α,β-unsaturated aldehyde **33** did not seem to be reactive at all, and even the ketone **42** did not show any conversion to the desired product **43**. The only product that was detected by ^{1}H NMR was the α,β-unsaturated imine (> 99% conv.) which did not react with a nucleophile boryl moiety to afford compound **43**. Generally, quaternary carbons are less reactive towards β-boration due to the steric hindrance of the substituent in the α-position. Therefore, it can be concluded that most likely the steric hindrance of the methyl moiety of **42** affected the whole reactivity. On the other hand, the acyclic compounds **44** and **48** were demonstrated to be suitable towards the borylation, with full conversion into **45** and **49**, respectively was observed. Only α-methyl-*trans*-cinnamaldehyde **46** did not react, possibly because of the presence of the methyl group in the vicinal position. All the compounds that have been synthesized during this comparative study (Scheme 3.9) have not been isolated and the formation of the relative products was determined analysing the crude mixture by ^{1}H NMR.

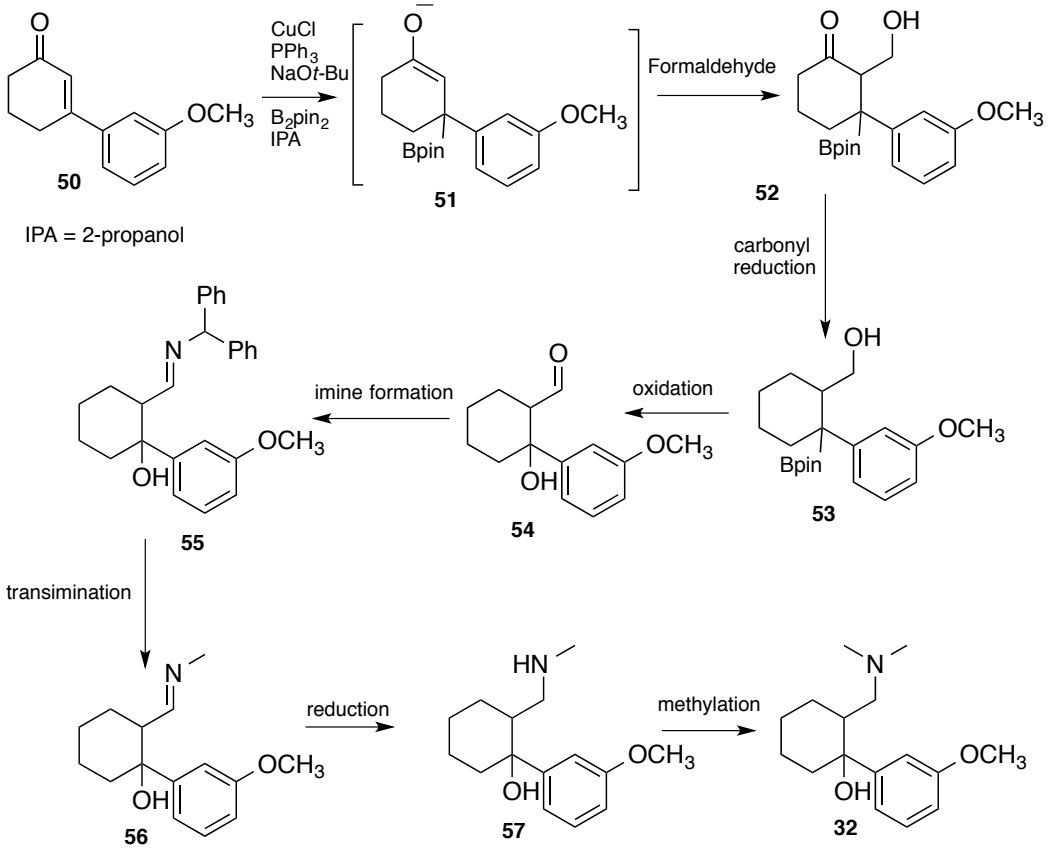
Some hypotheses have been put forwards regarding the lack of reactivity of those compounds that did not show any borylated product. Even though α,β-unsaturated compounds with a structure like the one shown in Fig. 3.2 are conjugated through the corresponding π-system, the single bond adjacent to the carbonyl or imine functional groups has rotational freedom that make it possible for it loose the orbital overlap required for conjugation, and therefore, the activation and subsequent reactivity at the β-position.



x= O, N

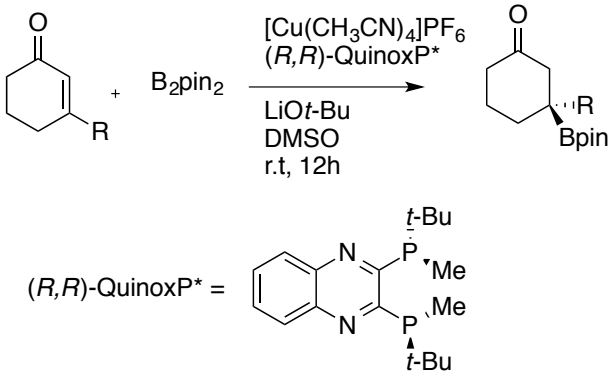
Fig. 3.2 Structure of unreactive α,β-unsaturated ketones and imines; the rotation around the single bond may explain the lack of reactivity.

In view of these considerations, a different kind of substrate was, therefore, evaluated via a related pathway for the Tramadol synthesis (Scheme 3.10).



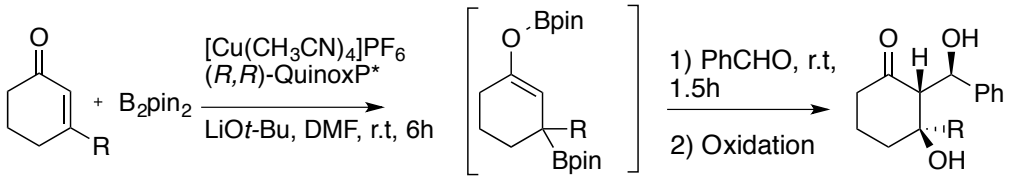
Scheme 3.10 Tandem conjugation boration/aldol reaction towards the synthesis of Tramadol.

This new pathway was inspired by work reported by Shibasaki and co-workers[8] in 2009. They reported the β-boration of β-substituted cyclic enones using a copper catalyst, modified with a chiral phosphine such as (*R*,*R*)-Quinox-P* (Scheme 3.11).



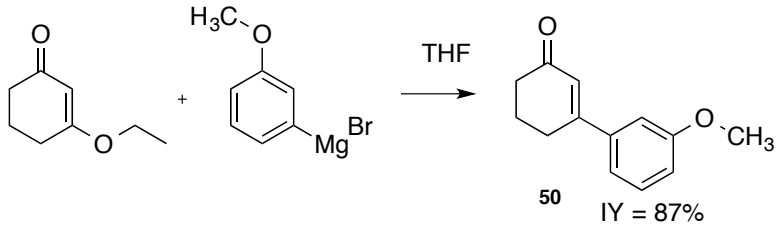
Scheme 3.11 β-Boration of β-substituted α,β-unsaturated enones using (*R*,*R*)-Quinox-P* as a chiral ligand.

Interestingly, since the reaction was carried out in a non-protic solvent such as DMSO or DMF, further transformations were performed. In fact, under these conditions, the intermediate boron enolate formed through the addition of the nucleophilic boron unit could react with a suitable electrophile. In particular, they developed an asymmetric tandem conjugated aldol addition using benzaldehyde as electrophile (Scheme 3.12).



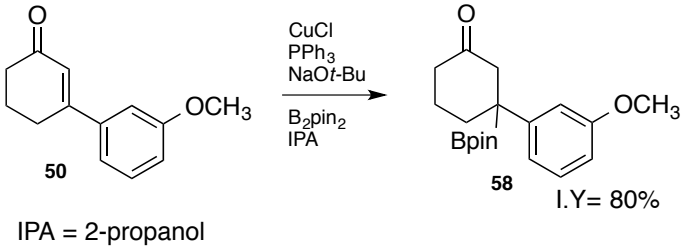
Scheme 3.12 Asymmetric tandem conjugation/aldol reaction using benzaldehyde as electrophile.

Therefore, the first part of this new approach was the synthesis of the starting material **50** (Scheme 3.13) according to a procedure reported in the literature,[9] which resulted in an 87% yield of the required enone **50**.



Scheme 3.13 Synthesis of the starting material **50** (I.Y = 87%).

α,β-Unsaturated ketones are generally not affected by the competitive 1,2-addition to the carbonyl group by the boron moiety under standard borylation conditions, unlike aldehydes. Indeed, compound **50** seemed to be more reactive, and hence, suitable for the β-boration. This improved reactivity of **50** over previous enone and enal systems can be explained by the fact that the carbonyl group is located in the cyclohexenyl ring and, therefore, no rotational effects are present in the molecule in order to break the activating π-conjugation effects at the β-position. In fact, when compound **50** underwent β-boration, the corresponding product **58** could be isolated in high yield (80 %) (Scheme 3.14).

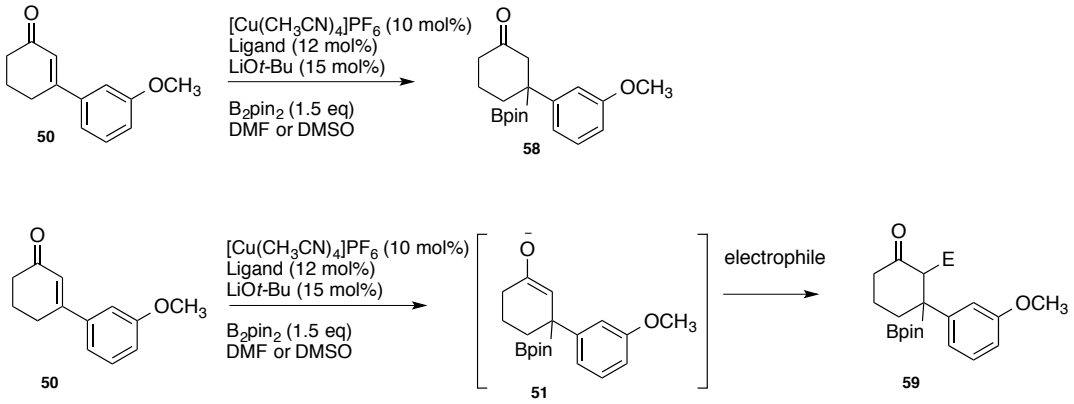


Scheme 3.14 Copper catalyzed β-boration of the enone **50**.

Through the synthetic route shown in Scheme 3.10, it should have been possible to overcome all the problems related to the low reactivity of **26**, which are connected to the rotational effect mentioned above (see Fig. 3.2). Even though the β-boration was successful in providing the product **58** in high yield (Scheme 3.14), the aim of this new approach was to generate the enolate species **51** (Scheme 3.10) *in situ* through borylation and trap directly via a tandem conjugated aldol reaction with a

formaldehyde equivalent to give **52**. In this context, following a slightly different procedure from the one reported by Shibasaki and co-worker,[8] compound **50** was added to a mixture of CuCl (3 mol%), PPh_3 (10 mol%), NaO*t*-Bu (15 mol%) and B_2pin_2 (1.1 eq) in 2-propanol to which, after 6 hours, a solution of formaldehyde in water was added before working up the reaction.

However, the ^1H NMR of the crude product showed the complete conversion of **50** into the β-borated product **58** without showing any formation of **52** (see Scheme 3.10). This seems to be reasonable according to the fact that in protic media (like 2-propanol), the protonation is a fast step. Therefore, the experiment was repeated and the formaldehyde was added at the same time as the substrate, followed by catalyst and diboron reagent, to see if the addition of the electrophile could compete with the protonation step. Unfortunately, the protonated product **58** was the only one detected by ^1H NMR. For this reason, a different catalytic system was considered, and in particular, one similar to one reported in literature.[8] Therefore, another copper source was evaluated, i.e. $[Cu(CH_3CN)_4]PF_6$ (Scheme 3.15).



Scheme 3.15 β-Borylation and tandem conjugated boration/aldol reaction.

Attempts were made to synthesize **58** by direct borylation of **50** using different ligands. The racemic version was initially carried out with PPh_3 and also rac-BINAP in DMF, but no conversion was observed in either case. A chiral approach was considered in the hope that such a system might be more catalytically reactive. Hence, initially, (*R*)-BINAP and (*R*)-DM-BINAP were tested as possible ligands, but in both cases, the conversion was negligible. For this reason, the same conditions for the reaction reported in the literature[8] needed to be reproduced to check that this reaction was as expected. Hence, a mixture of $[Cu(CH_3CN)_4]PF_6$ (10 mol%), (*R*,*R*) Quinox*P (12 mol%), B_2pin_2 (1.5 eq) and **50** (0.1 mmol) in DMF or DMSO was stirred for 10 minutes under argon, and then LiO*t*-Bu (15 mol%) was added. The solution changed from an orange colour to a dark green after the addition of the base, and the mixture was left stirring overnight. The best results, in terms of conversion into compound **58** (50%), were obtained using DMSO as a solvent. Since we were not interested in isolating compound **58** from the reaction mixture, only the conversion (50%) was determined (by ^{1}H NMR).

Therefore, attempts were then made to get the product **59** using benzaldehyde as electrophile via the process outlined in Scheme 3.15. The same procedure as that reported in the literature above was used and, after 6 hours (after base was added), 2.5 eq. of benzaldehyde was introduced. The reaction was stirred for another 1.5 hours and then worked up. Unfortunately, the ^{1}H NMR did not show any formation of the desired product and only unreacted benzaldehyde and starting material **50** were recognizable from the spectrum. With this information in hand, it was planned to run the reaction again at a higher temperature (50 °C), in order to force the conversion towards the formation of adduct **59**. However, in those cases, the desired product could not be formed and only the starting material **50** was found in the crude mixture. Another point that was considered was the use of a different electrophile to make a shorter pathway for the synthesis. Therefore, the addition of Eschenmoser's salt **60** (Fig. 3.3) to the intermediate **51** seemed to be ideal and the

most reasonable process in order to obtain the compound **67** after C=O reduction/C-B oxidation (Scheme 3.16).

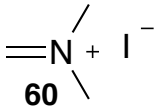


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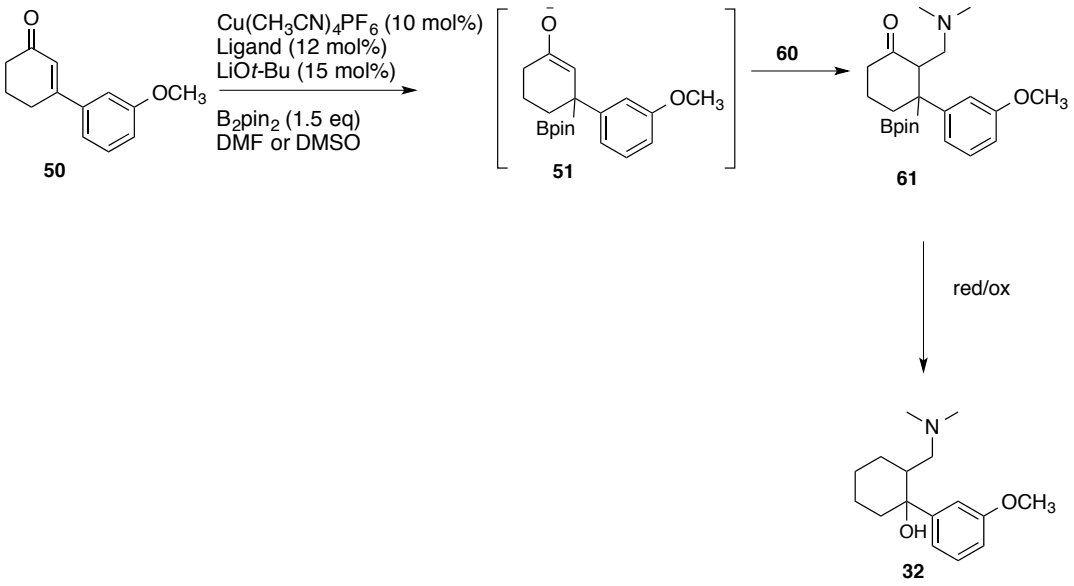
Fig. 3.3 Eschenmoser's salt



Scheme 3.16 Tandem conjugated boration/aldol reaction using **60** as electrophile.

A small solvent screening was carried out using PPh_3 as ligand and CuCl as catalyst, and three different solvents were tested, which were: 2-propanol; THF; and DMF. Compound **50** was then added to a solution containing CuCl, PPh_3, NaO*t*-Bu and B_2pin_2 in 0.5 mL of solvent. The reaction was left stirring for 6 hours and after that the reagent **60** was added then left overnight at r.t. The solubility of the Eschenmoser's salt was seen to be an issue, being only slightly soluble in 2-propanol. When the conversion was checked by ^1H NMR, no desired product **61** was detected in the crude mixture, which only contained the unreacted starting material **50**.

As this pathway seemed to be the quickest way to obtain **32**, another experiment conducted at a higher temperature was also carried out. Hence, the reaction was repeated and after the addition of the electrophile **60**, it was heated to 50 °C. After 16 hours, the mixture was analyzed by ^{1}H NMR, but in this case the desired product **61** could not be detected again showing only the unreacted staring material **50**.

In conclusion, this pathway was not successful at achieving the desired product Tramadol. Even though it has been possible to perform the β-boration of compound **50** under new conditions, the most delicate step related to the possibility of trapping out the enolate intermediate **51** with different formyl or equivalent electrophiles proved to particularly challenging and remains to be solved.

3.4 Conclusions

In this chapter we tried to exploit the boron chemistry and, in particular, the β-borylation reaction towards the synthesis of the bioactive compound Tramadol. We tried to develop a methodology consisting of the *in situ* formation of an α,β-unsaturated imine intermediate, one-pot β-boration, transamination, reduction and oxidation. Unfortunately, after several attempts we could not achieve our goal.

We tried both catalytic and organocatalytic protocols to achieve the most challenging step that demonstrated to be the β-borylation of the imine intermediate.
In order to investigate further into the reasons why α,β-unsaturated imines deriving from **26** and **33** were not reactive to the standard conditions for the β-boration, some experimental studies were carried out. As mentioned in this chapter, compounds that have a single bond with remarkable freedom of rotation adjacent to

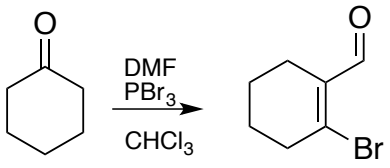
a C=N double bond are much less reactive towards the β-boration than those that are not affected from this conformational issue.

In fact, compounds **44** and **48** (Scheme 3.9) and the enone **50** reacted (Scheme 3.14) smoothly to give the corresponding β-borated products. Even though the total synthesis of Tramadol could not be achieved, it was possible to investigate the reactivity of a range of α,β-unsaturated ketones and imines and then to explain why the relative pathways towards the synthesis of Tramadol were not successful.

3.5 Experimental part

All reagents were used as received from the supplier without further purification, unless stated. All solvents were used as received from the supplier, except THF (freshly distilled), methanol and 2-propanol (stored over molecular sieves). Molecular sieves, 3Å 1-2mm beads, were supplied from Alfa Aesar, and stored at 220 °C. Reactions were monitored by TLC analysis using POLTFRAM® SIL G/UV254 (40 x 80 mm) TLC plates. Flash column chromatography was carried out using silica gel as supplied from Sigma-Aldrich (230-400 mesh, 40-63 μm, 60 Å) and monitored using TLC analysis.^{1}H NMR spectra were recorded on a Varian-Mercury 500 MHz spectrometer, operating at ambient probe temperature unless specified elsewhere. ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz instrument, operating at 100.6 MHz, unless specified elsewhere. Deuterated chloroform $CDCl_3$ was used as solvent for all NMR spectra, unless specified elsewhere. NMR peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), combinations thereof, or as a multiplet (m).
All "*in situ*" IR spectroscopy experiments (ReactIR) were performed by using a ReactIR 15 instrument with a mercury-cadmium-tellur-ide detector, a Happ–Genzel function, and a DiComp (diamond) probe connected through an AgX 9.5 mm–2 m fibre over 2500-650 cm^{-1} with 8 wavenumber resolution.

Synthesis of 2-bromocyclohex-1-enecarbaldehyde[7]



Phosphorous tribromide (2.60 mL, 27.5 mmol) was added to a solution of DMF (2.4 mL, 30.6 mmol) in $CHCl_3$ (20 mL) at 0 °C. After 30 minutes, the reaction mixture was warmed to RT and a solution of cyclohexenone (1.05 mL, 10.2 mmol) in $CHCl_3$ (10 mL) was added.

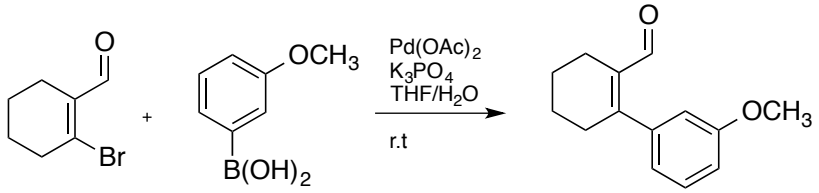
The reaction mixture was heated at reflux for 3 hours, cooled to RT and poured onto ice and water (50 mL). Solid sodium bicarbonate was added to neutralize the aqueous phase, which was separated and extracted with DCM. The combined organic phases were washed with sat. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by silicagel chromatography (40:1, petroleum ether/ethyl acetate as eluent) afforded the pure product (843 mg, 44%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 2.78-2.74 (m, 2H), 2.32-2.27 (m, 2H), 1.81-1.67 (m, 4H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.7, 143.8, 135.3, 38.8, 25.0, 24.27, 21.10

All spectroscopic and analytical properties were identical to those reported in the literature[7]

Synthesis of 2-(3-methoxyphenyl)cyclohexanecarbaldehyde



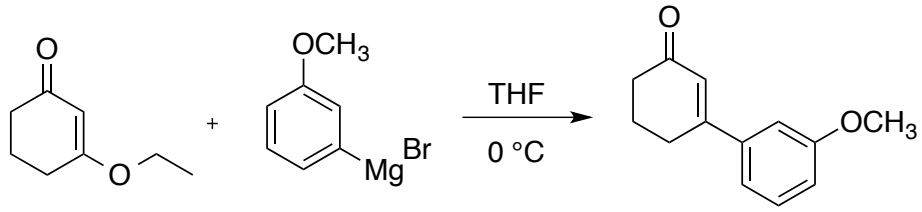
To an aqueous solution of K_3PO_4 (2.6 mL, 2M) was added $Pd(OAc)_2$ (3.0 mg, 0.5 mol%) followed by a solution of 2-bromocyclohex-1-enecarbaldehyde (2.6 mmol) and 3-methoxy-phenyl boronic acid (3.12 mmol) in THF (5mL). The reaction mixture was stirred vigorously at r.t. and after 3 hours was diluted with water (10 mL) and extracted with Et_2O (10mL X 3), dried with $MgSO_4$ and concentrated under reduced pressure.

Purification by chromatography (10:1, petroleum ether/ethyl acetate) afforded the pure product (474 mg, 82% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.32 (m, 1H), 6.92 (dd, J= 2.6, 0.9 Hz, 0.5H), 6.91 (dd, J= 2.6, 0.9 Hz, 0.5H), 6.84-6.83 (m, 1H), 6.82-6.81 (m, 1H), 6.78-6.77 (m, 1H), 3.84 (s, 3H), 2.57-2.53 (m, 2H), 2.38-2.34 (m, 2H), 1.82-1.70 (m, 4H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.6, 159.3, 159.1, 140.9, 135.7, 129.2, 121.2, 114.2, 113.6, 55.31, 33.9, 22.4, 22.2, 21.4

Synthesis of 3'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one[9]

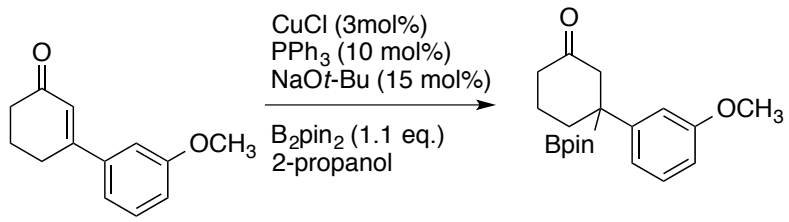


An oven-dried flask was charged with 3-methoxyphenylmagnesium bromide (42.8 mL, 42.8 mmol, 1.0 M in THF) and cooled to 0 °C. 3-Ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) was added to the Grignard reagent, dropwise. Once the addition was complete, the reaction mixture was left at RT until complete disappearance of the starting material. After 24 h, the reaction was slowly quenched with a solution of HCl (1 M, 100 mL). The aqueous phase was separated and extracted further with AcOEt (25 mL) (3x). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$, brine and water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by silicagel chromatography (petroleum ether/AcOEt, 8:1 as eluent) to provide the title compound as a yellow oil (3.76 g, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J= 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 7.07-7.06 (m, 1H), 6.99-6.96 (m, 1H), 6.44 (t, J= 1.4 Hz, 1H), 3.86 (s, 3H), 2.79 (td, J= 6.1, 1.4 Hz, 2H), 2.52-2.49 (m, 2H), 2.21-2.14 (m, 2H).
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.9, 159.9, 159.6, 140.3, 129.7, 125.6, 118.5, 115.4, 111.7, 55.3, 37.3, 28.2, 22.8

All spectroscopic and analytical properties were identical to that reported in the literature.[9]

Synthesis of 3-(3-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone



In an oven-dried schlenk 2-propanol was added to CuCl (1.5 mg, 0.075 mmol), PPh_3 (13 mg, 0.05 mmol), NaO*t*-Bu (7.2 mg, 0.075 mmol), B_2pin_2 (140 mg, 0.55 mmol) and the mixture stirred for 10 min under argon. Then the substrate **29** (101 mg, 0.5 mmol) was added and the reaction was left stirring at room temperature for 16 h.

So the reaction was diluted with AcOEt (5mL) and water (2 mL) and the aqueous phase was extracted with AcOEt (3x).

The organic phase was then dried with $MgSO_4$, filtered and concentrated *in vacuo*.

Purification by chromatography (Petroleum Ether/AcOEt 8:1) afforded the titled compound as colorless oil (132 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J= 8.0 Hz, 1H), 6.90-6.87 (m, 2H), 6.75 (dd, J= 2.5, 0.8 Hz, 0.5H), 6.73 (dd, J= 2.5, 0.9 Hz, 0.5H), 3.81 (s, 3H), 2.87 (dt, J=14.1, 1.5 Hz,1H), 2.61-2.57 (m, 1H), 2.41-2.26 (m, 3H), 2.02-1.90 (m, 2H), 1.86-1.76 (m, 1H), 1.18 (d, J= 3.2 Hz, 12H).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.3, 159.6, 146.2, 129.3, 118.7, 112.3, 111.0, 83.9, 55.1, 48.5, 41.1, 33.2, 24.5, 23.7.

^{11}B NMR (128.3 MHz, $CDCl_3$) δ 32.6

3.6 References.

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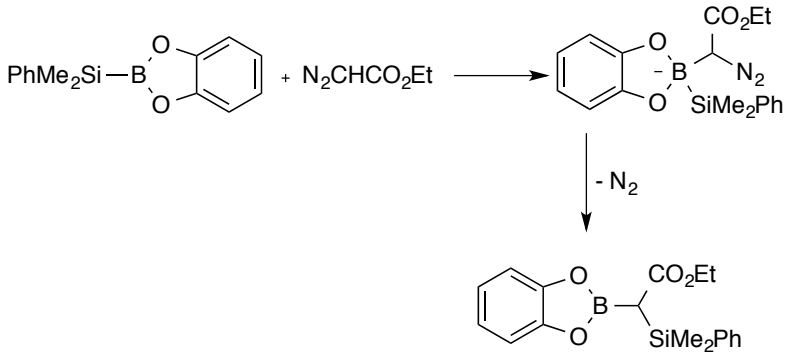
UNIVERSITAT ROVIRA I VIRGILI
SELECTIVE POLYFUNCTIONAL SYNTHESIS THROUGH ORGANOBORON COMPOUNDS
Enrico La Cascia

Chapter 4

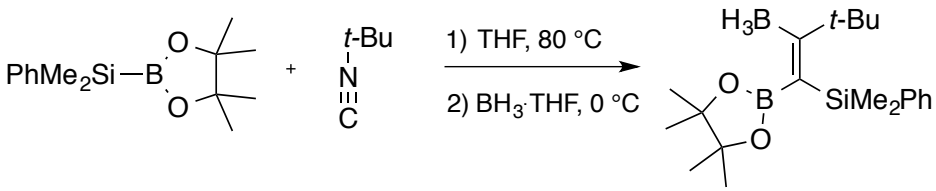
Gem-silylborylation of carbonyl compounds to generate *in situ* selective tetrasubstituted olefins.

4.1 Scope of the art on the synthesis of *gem*-silylboronates and their applications.

Geminally functionalized carbon atoms with Si-B interelement substituents represents a suitable transition-metal-free platform to prepare C(sp^3)(B)(Si) compounds.[1] This reactivity was first explored by Buynak and Geng in 1995,[2] and it's initiated by the interaction of ethyl diazoacetates with the empty *3p* orbital of the B atom in Me_2PhSi-Bcat (Bcat= catecholboryl moiety) forming an 'ate' complex (Scheme 4.1). More recently, Wang and co-workers have revisited the subject providing the synthesis of 1-silyl-1-boryl compounds via reaction of the corresponding *N*-tosylhydrazones and $Me_2PhSiBpin$ (Bpin= pinacolboryl moiety) under thermal conditions.[3] Suginome, Ito et al., found that the insertion of alkyl and aryl isonitriles into the silicon-boron bond of silylboranes could also proceeded thermally to provide (boryl)(silyl)iminomethanes in moderate to good yields (Scheme 4.2).[4]

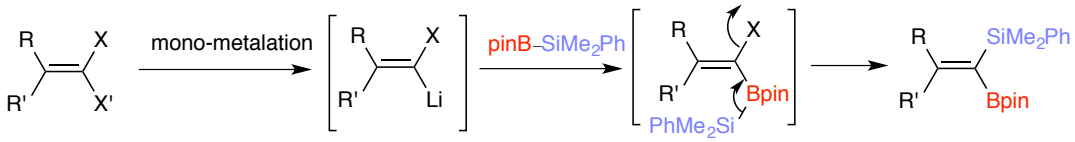


Scheme 4.1 Insertion of ethyl diazoacetates into B-Si bond.



Scheme 4.2 Insertion of isonitriles into Si-B bond.

Several interesting *gem*-silylborylation protocols have been developed by reaction of vinylic halides with Me_2PhSi-Bpin in the presence of lithiated bases. This methodology, developed by Hiyama and Shimizu, affords 1-boryl-1-sylilalkanes,[5] 1-boryl-1-silylallenes,[6] and 1-boryl-1-sylilalkenes[7] (Scheme 4.3).

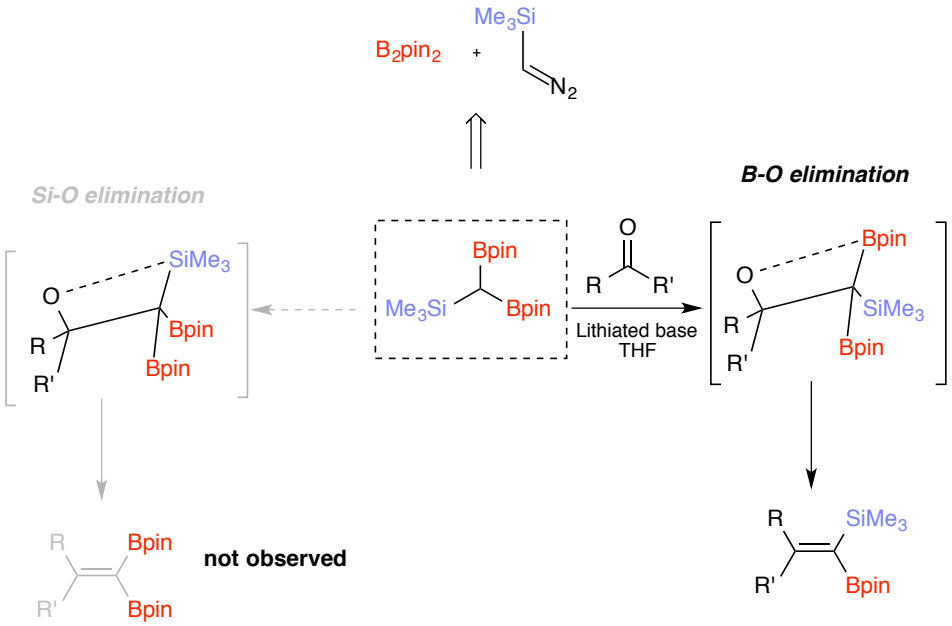


Scheme 4.3 Synthesis of *gem*-silaborated olefins.

The latter example is of fundamental interest, since the access to *gem*-difunctionalization of alkenes becomes a direct method towards substituted olefins through stereodivergent protocols.

4.2 Work hypothesis

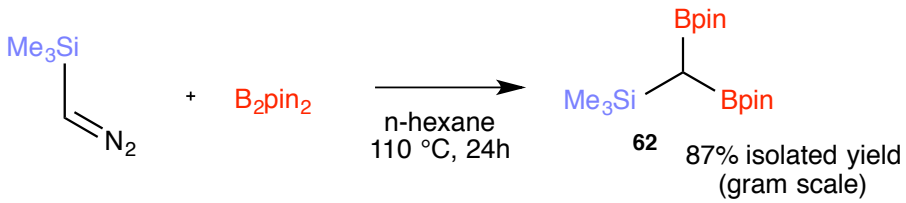
In that context and considering our ongoing research based on metal-free insertions of diazo synthons into sigma non-symmetric B-B bonds[8] and B-S bonds,[9] we wish to study an innovative and straightforward insertion of the commercially available (trimethylsilyl)diazomethane reagent into bis(pinacolato)diboron (B_2pin_2). The corresponding multisubstituted $HC(Bpin)_2(SiMe_3)$ product, could be eventually deprotonated in the presence of lithiated bases, generating a boron and silicon stabilized carbanion, able to attack a carbonyl function, as an attractive entry point to olefination of carbonyl compounds. In fact we wish to explore that, upon such addition, two possible eliminations could take place: the classical Peterson-type Si-O elimination (Scheme 4.4, left) to afford a *gem*-diboron product or the B-O elimination to access the *gem*-silaborated structures (Scheme 4.4, right). Some previous examples about the feasibility of the stereoselective B-O *syn*-eliminations have been reported by Endo, Shibata and Morken.[10,11]



Scheme 4.4 Strategic synthesis of *gem*-silylboronates.

4.3 Results and discussion

The synthesis of $HC(Bpin)_2(SiMe_3)$ **62** can be efficiently obtained in a gram scale simply by mixing 1eq of B_2pin_2 and 2eq of (trimethylsilyl)diazomethane (2*M* hexane solution), heating the mixture at 110 ºC for 24h. (Scheme 4.5)
The product was purified by flash chromatography (hexane/ethyl acetate = 40/1) with an isolated yield of 87% as white solid. The ^{11}B NMR spectra shows a broad signal at 33.2 ppm while the ^{29}Si NMR spectra has a signal at 2.0 ppm.



Scheme 4.5 Direct synthesis of $HC(Bpin)_2(SiMe_3)$ **62** in gram scale.

Next we initiated the study on deprotonation of $HC(Bpin)_2(SiMe_3)$ with lithiated bases, to promote their reaction with carbonyl group.
We tentatively examined the deprotonation of **62** with cyclohexanone by adding lithium 2,2,6,6-tetramethylpiperidine (LiTMP) to **62**, in THF at 0 ºC, followed by addition of the cyclohexenone and subsequent warming up to room temperature for 2h. After the work up and chromatography, the *gem*-silylboronate product **63** was isolated in 95% (Table 4.1, entry 1). Similarly, excellent reactivity was exhibited by a series of 4-substituted cyclohexanones, affording the corresponding symmetric *gem*-silaborated alkenes **64-67** in very good yields (Table 4.1, entries 2-5). The use of 1.2 equiv of the base was found necessary, as the reaction proved to be less efficient when this amount was reduced to 1.0 equiv (Table 4.1, entry 6). Next, we applied the silylborylation protocol to 3-methylcyclohexanone. In this case a nearly

quantitative formation of the *gem*-silylborylated products **68/68'** took place (Table 4.1, entry 7), albeit as a 55:45 mixture of the two possible stereoisomers. Interestingly, 2-methylcyclohexanone lead to the *gem*-dimetalated products **69/69'** in 70% isolated yield and a synthetically useful 70:30 (*E*/*Z*) stereoisomeric ratio (Table 4.1, entry 8) in favour to the isomer with $SiMe_3$ close to the ortho-Me position. Polarization transfer NMR experiments to determine the configuration of **69** were carried out. Based on the 1D selective NOE experiments the configuration of isomer **69** was confirmed (Fig. 4.1).

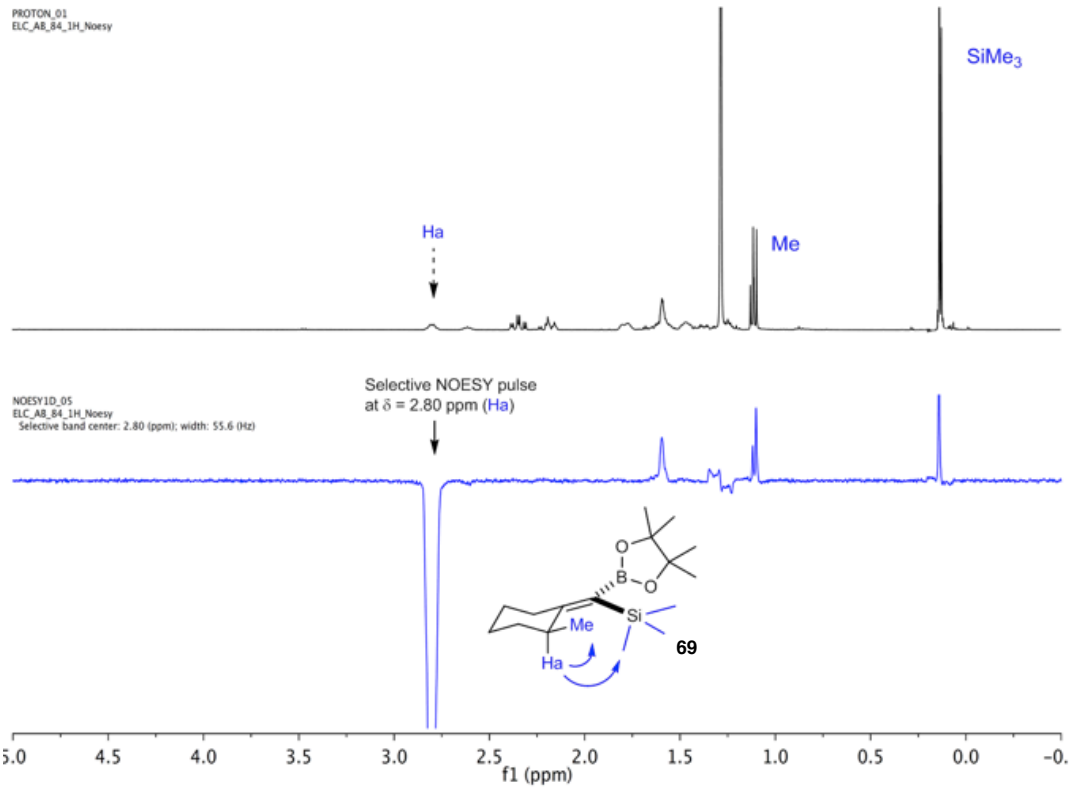
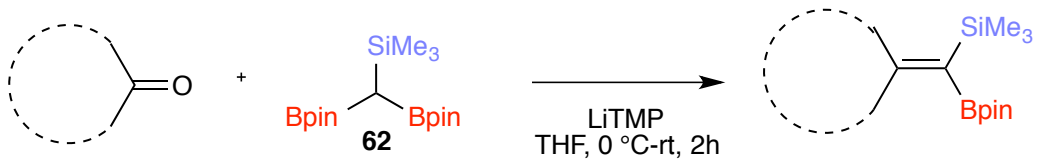


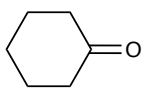
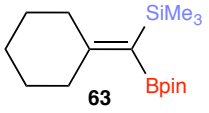
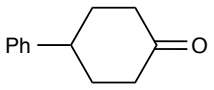
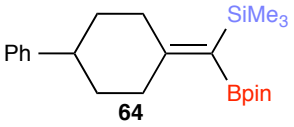
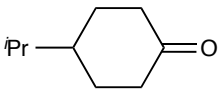
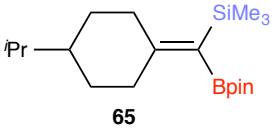
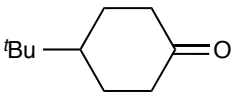
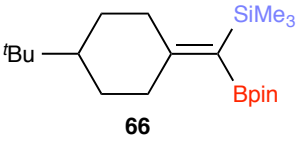
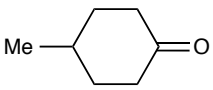
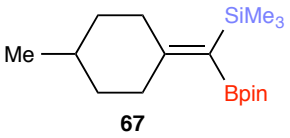
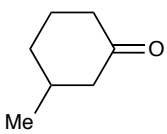
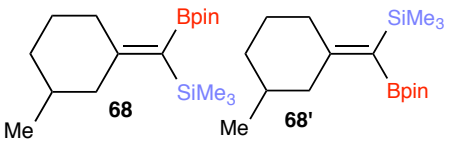
Fig. 4.1 1D Selective NOE NMR experiment to determine the configuration of the isomer **69**.

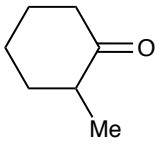
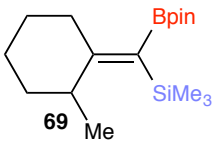
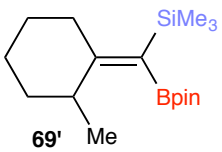
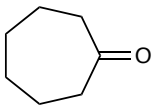
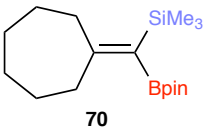
The protocol for olefination of cyclic ketones by reaction with $^{-}C(Bpin)_2(SiMe_3)$ is also applicable to larger size ketones, such as cycloheptanone, providing the

corresponding silylboronate product **70** in moderate isolated yield (Table 4.1, entry 9).

Table 4.1 *Gem*-silylborylation of cyclic ketones with **62** [a]



Entry	Substrate	Product	NMR Yield (%)[b]	Isolated yields[%] (X/X')[c]
1		 **63**	97	95
2		 **64**	85	83
3		 **65**	89	87
4		 **66**	84	82
5		 **67**	95	88
6[d]			60	55
7		 **68** **68'**	95	90(55/45)

8		 	75	70(70/30)
9			60	56

[a] Reaction conditions: **62** (0.1 mmol), ketone (0.15 mmol, 1.5 eq.), LiTMP (0.12 mmol, 1.2 eq.), THF (0.2 mL), from 0 °Cto rt for 2h. [b] Yields were determined by ^{1}H NMR analysis of the crude of reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c] Stereoisomeric Ratio. [d] **62** (0.1 mmol, 1 eq.), ketone (0.1 mmol, 1 eq.), LiTMP (0.1 mmol, 1 eq.).

We next, explored the *gem*-silylborylation of non cyclic ketones and we found that cyclopropyl(phenyl)methanone was easily converted to the corresponding *gem*-silylboronate product regardless the amount of reagent **62** used (Table 4.2, entries 1,2). Interestingly, the reaction is performed with high stereoisomeric ratio (**71**/**71'** = 95/5) being the major isomer formed the one with the Bpin moiety *cis* to the Ph group.

Polarization transfer NMR experiments to determine the configuration of compound **71** were carried out. Based on the 1D selective NOE NMR experiments, the assignment of isomer **71** was confirmed (Fig 4.2).

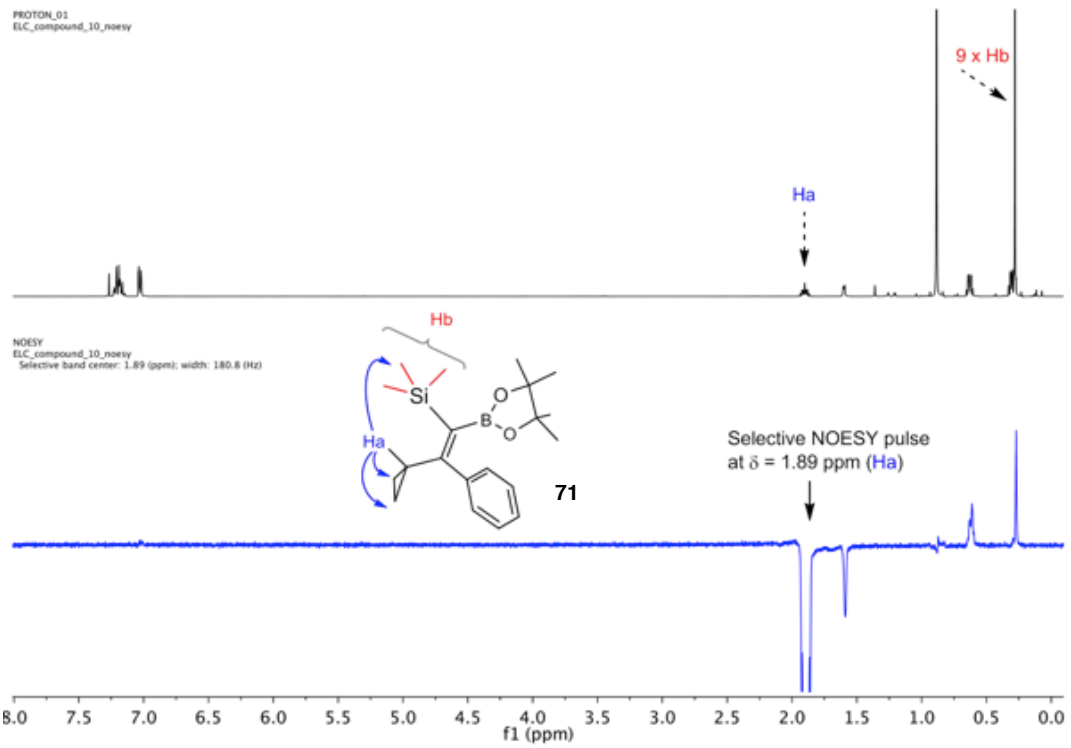
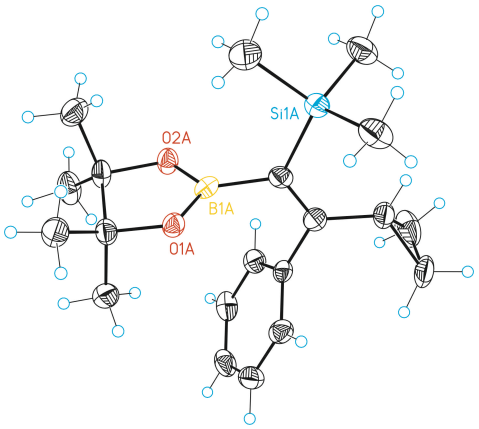


Fig 4.2 Assignment of the configuration of **71** through 1D selective NOE NMR experiment.

The X-Ray diffraction of **71** could also be carried out providing more specific data about the distances between cyclopropyl and the $SiMe_3$ group (Fig. 4.3).

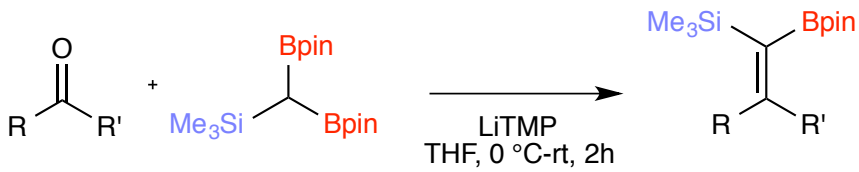


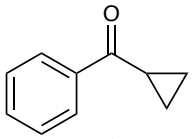
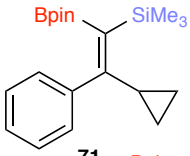
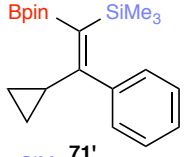
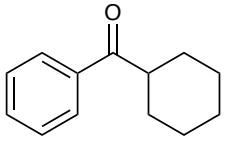
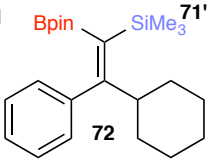
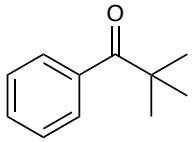
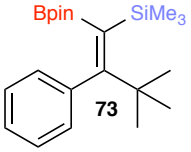
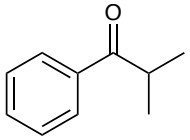
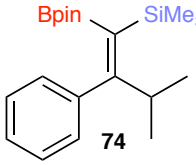
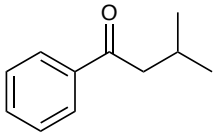
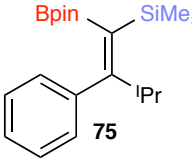
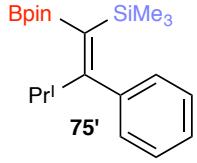
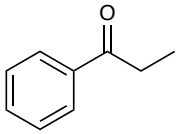
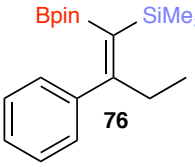
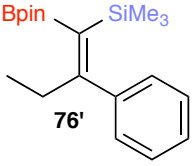
d(Si-C)=1.874(3)Å
d(B-C)=1.552(5)Å
d(C=C)=1.354(4)Å

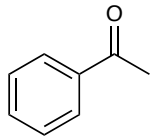
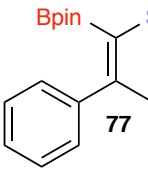
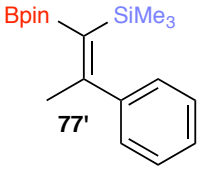
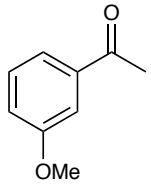
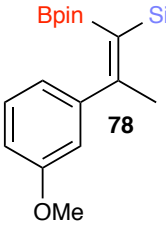
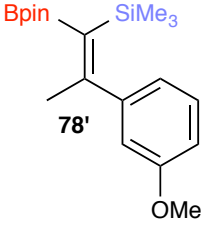
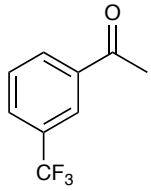
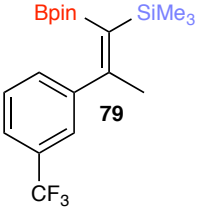
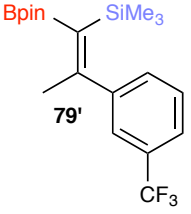
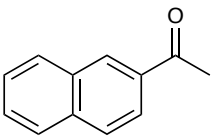
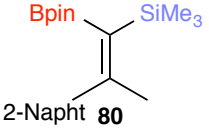
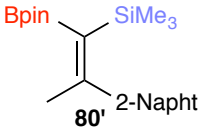
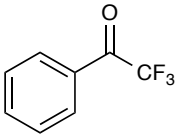
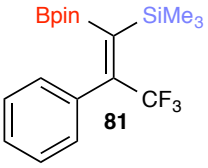
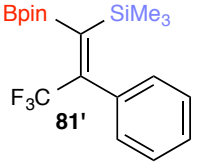
$\widehat{B\text{-}C\text{-}Si} = 117.9(2)°$

Fig 4.3 X-Ray structure of compound **71**.

Table 4.2 *Gem*-silylborylation of non-cyclic ketones with **62**[a]

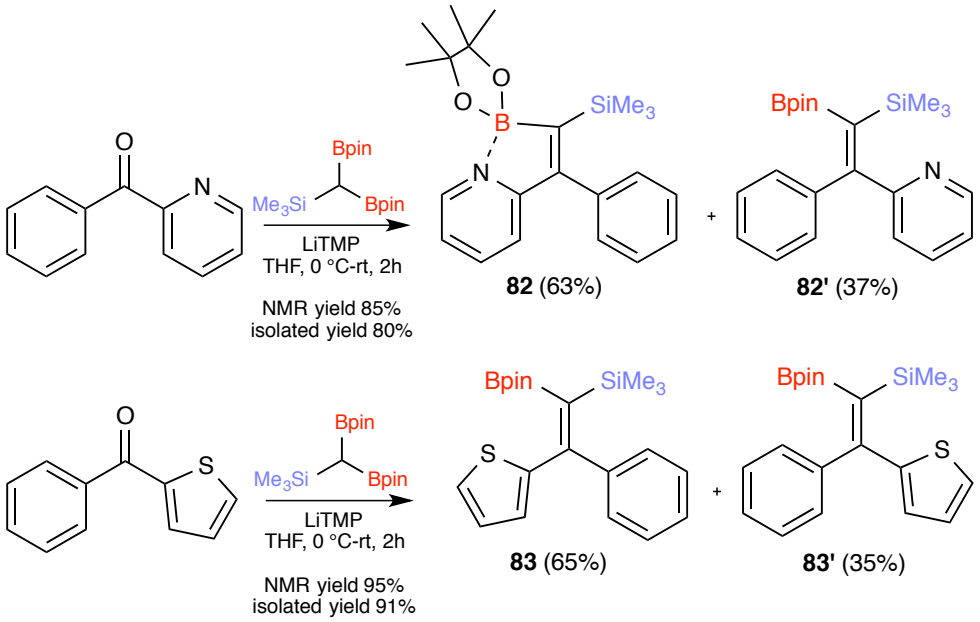


Entry	Substrate	Product	NMR yield (%)[b]	Isolated yields[%] (X/X')[c]
1		 **71**	92	87(95/5)
2[d]		 **71'**	93	89(95/5)
3		 **72**	87	86(99/1)
4		 **73**	55	52(99/1)
5		 **74**	70	67(99/1)
6		 **75**  **75'**	62	60(91/9)
7		 **76**  **76'**	44	40(90/10)

8		 **77**	 **77'**	42	40(87/13)
9		 **78**	 **78'**	44	42(89/11)
10		 **79**	 **79'**	73	70(87/13)
11[e]		 **80**	 **80'**	53	50(88/12)
12		 **81**	 **81'**	92	91(63/37)

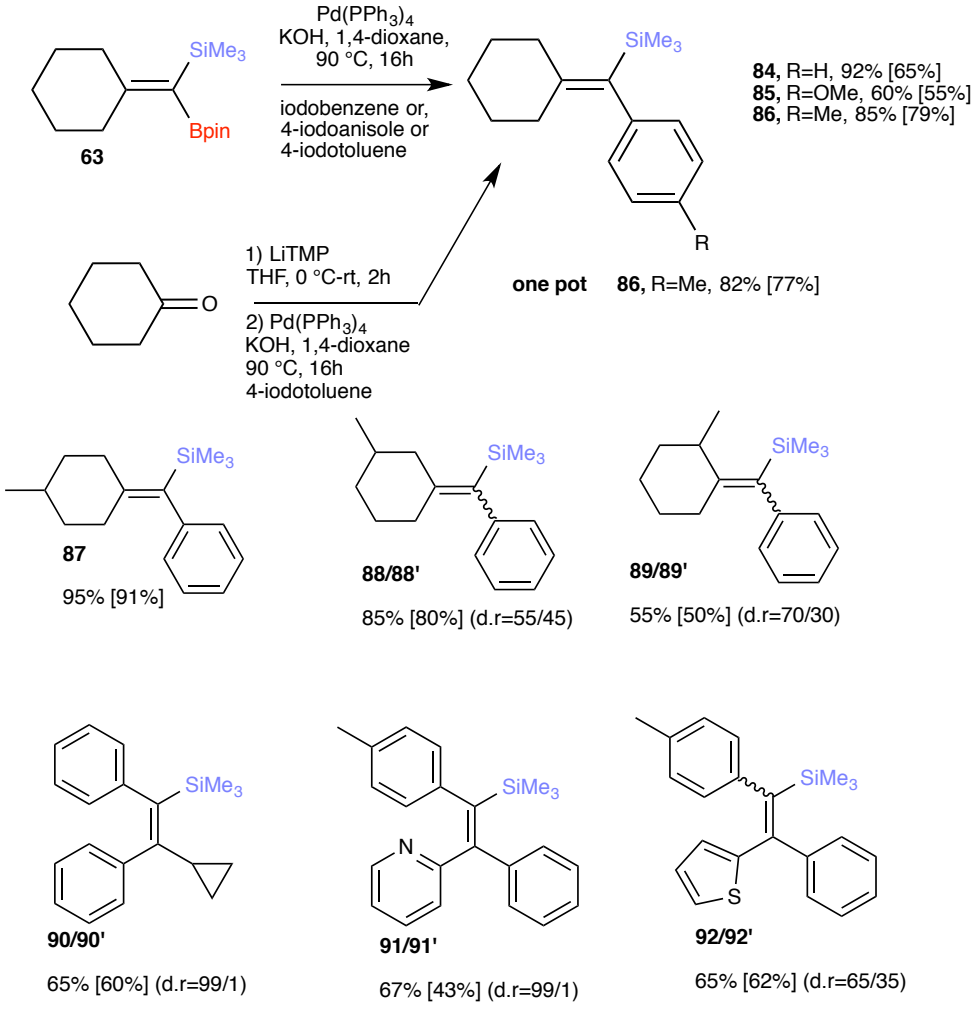
[a] Reaction conditions: **62** (1.2 eq.), ketone (1.0 eq, 0,1 mmol), LiTMP (1.4 eq), THF (0.2 mL), from 0 °C to rt for 2h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c]Stereoisomeric Ratio. [d] **62** (1.0 eq.), ketone (1.5 eq), LiTMP (1.2 eq.). [e] 2-napth = 2-naphthyl.

Even higher stereoselectivity has been observed in the reaction of hindered aliphatic ketones, such as cyclohexyl(phenyl)methanone, 2,2-dimethyl-1-phenylpropan-1-one and 2-methyl-1-phenylpropan-1-one, with a stereoisomeric ratio up to 99/1 in products **72**, **73** and **74** respectively (Table 4.2, entries 3-5). The less sterically hindered ketone 2-methyl-1-phenylbutan-1-one was also conveniently converted into the desired *gem*-silylboronate product but the stereoisomeric ratio slightly decreased (**75**/**75'** = 91/9) (Table 4.2, entry 6). This trend is extended to the *gem*-silylborylation of aryl(ethyl)ketone and aryl(methyl)ketones, independently of the electronic nature of the substituents on the aryl group (Table 4.2, entries 7-11). It can be seen that the corresponding *gem*-silylboronate products **76**–**80** were prepared in stereoisomeric ratios about (**X**/**X'** = 87-90/13-10) with moderate yields except in the case of products **79**/**79'** that were isolated up to 70% probably due to the enhanced reactivity of the ketone as a consequence of the electron withdrawing meta-substituent in the aryl group (Table 4.2, entry 10). Similar criteria might justify the quantitative transformation of the phenyl(trifluoromethyl)ketone into the *gem*-silylboronate products **81**/**81'** (isolated yield 91%) despite the fact that the stereoisomeric ratio lowered to 63/37, (Table 4.2, entry 12). When phenyl(pyridin-2-yl)methanone was transformed into the *gem*-silylborated products **82**/**82'**, the stereoisomeric mixture was 63/37 being the major isomer **82** the one with Bpin moiety *cis* to the pyridine group. The stereoisomer **82** was easily separated and isolated in pure form from the stereoisomeric mixture due to the notable interaction between N and B, making the compound more polar (Scheme 4.6). Compound **82** showed a characteristic ^{11}B NMR signal at 16 ppm, as a consequence of the B-N interaction. In contrast, the *gem*-silylborylation of phenyl(thiophen-2-yl)methanone provided the mixture of the stereoisomeric silylborylated products **83**/**83'**, but **83** could not be separated from **83'** since the S-B interaction was not observed in this particular case (Scheme 4.6).



Scheme 4.6 *Gem*-silylborylation of phenyl(pyridin-2-yl)methanone and phenyl(thiophen-2-yl)methanone with **62**.

Our next challenge was to use the *gem*-silylboronated products in the selective generation of tetrasubstituted olefins and towards this end we initiated the study by conducting Suzuki-Miyaura cross-coupling of **63** with iodobenzene or 4-iodotoluene, in the presence of $Pd(PPh_3)_4$, KOH, 1,4-dioxane as solvent, at 90ºC during 16h,[12] as standard reaction conditions. The *gem*-silylboronated product **63** was efficiently transformed into 1-aryl,1-trimethylsilyl-methylenecyclohexane products **84-86** (Scheme 4.7). To our delight, we also proved that the straightforward transformation of cyclohexanone into **86** could also be performed in a "one pot" sequence, via *gem*-silylborylation followed by Pd-cross coupling, without the need to isolate the *gem*-silylboronated products (Scheme 4.7).



Scheme 4.7 Cross-coupling of *gem*-silylborylated product **63** and sequential *one pot gem*-silylborylation/cross coupling of cyclohexenone.

With this convenient approach in our hands, we applied the "one pot" sequence to a representative type of cyclic and non-cyclic ketones. The *para*-methylcyclohexenone, followed the sequential one pot *gem*-silylborylation/cross coupling reaction providing the corresponding product **87** in high quantitative yield (Scheme 4.7). As expected, the *metha*- and *ortho*-methylcyclohexenones were transformed into **88**/**88'** and **89**/**89'** with lower stereoisomeric ratio (Scheme 4.7).

However, the non-cyclic ketone cyclopropyl(phenyl)methanone was stereoselectively transformed into the trisubstituted 1-silylalkenes **90** with good yield (Scheme 4.7). We also were able to prove that the B-N interaction on the *gem*-silylboronated product **82** assisted the selective cross coupling from the stereoisomeric mixture **82**/**82'** since **91** was the exclusive product formed and no traces of **91'** were detected (Scheme 4.7). On the contrary, the lack of interaction between B and S in the intermediates **83**/**83'** did not assist the stereoselective C-C bond formation and therefore the *gem*-silylborylation/cross coupling reaction of phenyl(thiophen-2-yl)methanone only gave moderate stereoselection of the trisubstituted 1-silylalkenes **92**/**92'** (Scheme 4.7). In order to confirm the configuration of the major stereoisomer **92**, polarization transfer NMR experiments were carried out. Based on the 1D selective NOE NMR experiments, the configuration of isomer **92** was confirmed (Fig. 4.4).

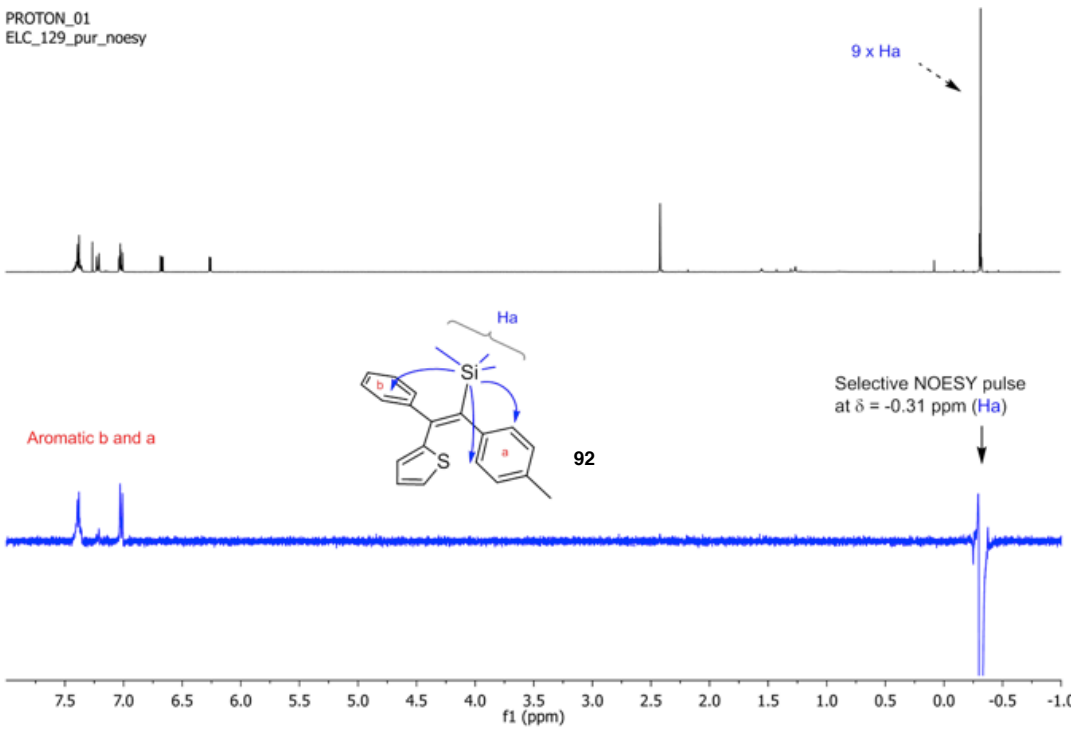
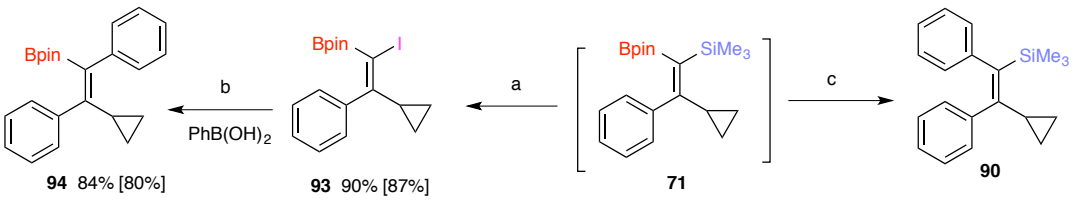


Fig 4.4 1D Selective NOE NMR experiment to determine the configuration of the isomer **92**.

This methodology complements the reported synthetic protocols based on the reactivity of alkylidene-type carbenoids with silylborane reagents followed by Suzuki-Miyaura cross coupling,[5] or iron catalyzed carbometalation ring opening of 1-trimethylsilylcyclopropenes,[13] or intramolecular *trans*-silylruthenation of internal alkynes and subsequent insertion of vinyl boronates[14] to address the most challenging task of tetrasubstituted alkene synthesis. Alternatively to the cross coupling of **71** toward 1-silylalkene **90**, we also conducted the most challenging silicon based cross-coupling, keeping the Bpin unit untouched. We proceed via iododesilylation[15] of **71** with $I_2/AgNO_3$ to obtain the desired product **93** with high yield, which was further reacted with $PhB(OH)_2$ in presence of Pd complex to access trisubstituted 1-borylalkene **94** with total control of stereoselectivity (Scheme 4.8).



Scheme 4.8 Stereochemical course of the sequential cross coupling via Suzuki-Miyaura and iododesilylation/cross coupling of **71**. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $PhB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h. [c]$Pd(PPh_3)_4$, KOH, 1,4-dioxane, 90 ºC, 16h.

Intermediate **93** could be fully characterized by polarization transfer NMR experiments and X-Ray diffraction to determine the configuration (Fig. 4.5 and Fig.4.6).

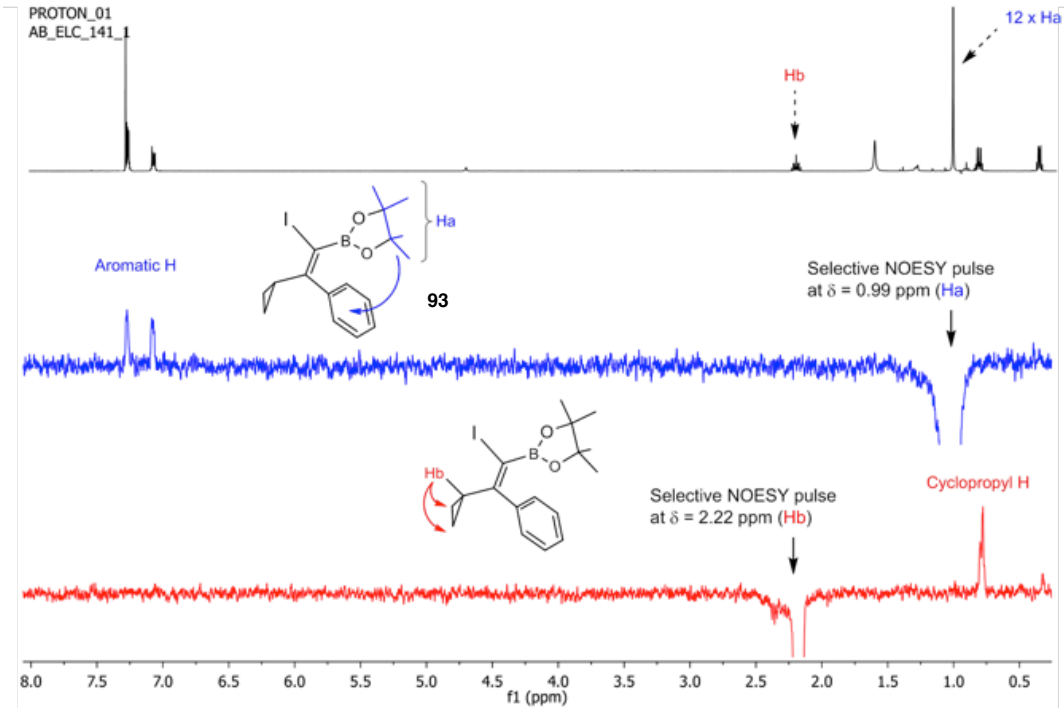
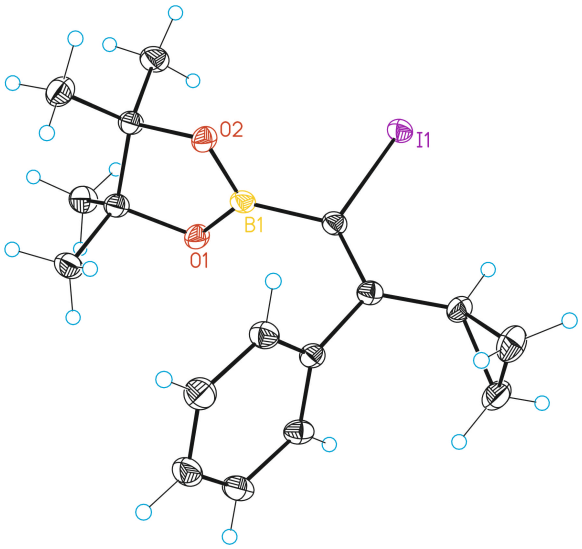


Fig. 4.5 1D Selective NOE NMR experiment to determine the configuration of the isomer **93**.

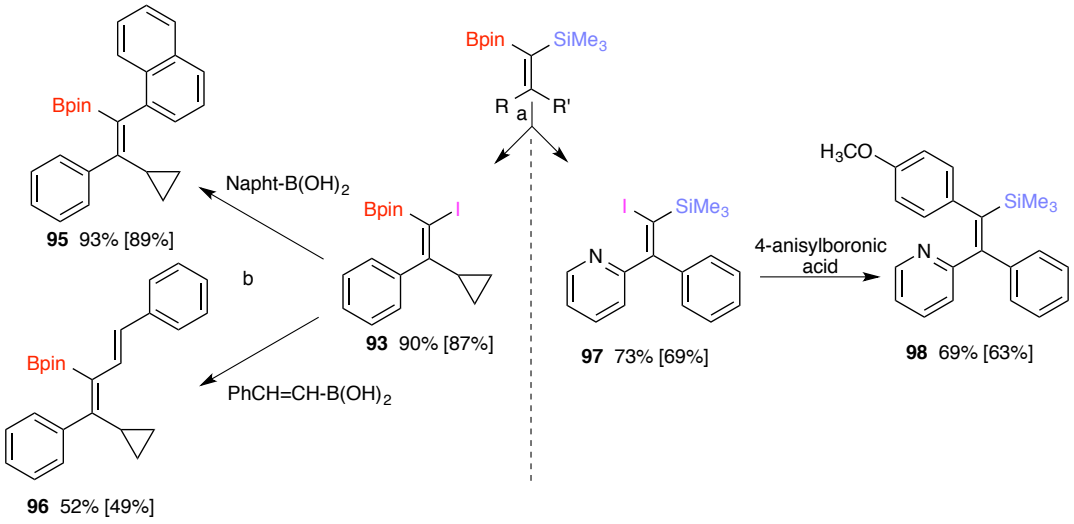


d(I-C)=2.126(2)Å
d(B-C)=1.560(3)Å
d(C=C)=1.348(3)Å

$\widehat{B\text{-}C\text{-}I}$=108.37°

Fig. 4.6 X-Ray structure of compound **93**.

To the best of our knowledge, this is the first example of selective silicon based cross-coupling in silylboronated products and its usefulness rely in the synthesis and stereoselective control of unusual trisubstituted 1-borylalkenes, such as products **95** and **96**, which were isolated from the reaction of **93** with naphtylboronic ester and vinylboronic ester, respectively (Scheme 4.9).



Scheme 4.9 Divergent iododesilylation/cross coupling reactions. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $RB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h

However, any attempt to iododesilylate the *gem*-silaborated product **82**, were unsuccessful and only the iododeborylated product **97** was observed, probably due to the interaction of N to B that assists the Bpin release (Scheme 4.9). The reactivity of **97** with 4-anisylboronic acid allowed to isolate the trisubstituted 1-silylalkene **98** with total stereocontrol (Scheme 4.9).

Based on the new stepwise protocol to selectively functionalize the *gem*-silaborated products, we finally conducted the synthesis of tetrasubstituted olefins with total control of the stereoselectivity. To prove the concept, compound **99** was efficiently isolated from the reaction of **94** with 4-iodoanisole in presence of $Pd(PPh_3)_4$, and more remarkably, the challenging[16] all-carbon tetrasubstituted alkenes **100** and

101 were also generated from **95** and **96** via Pd mediated cross coupling with 4-iodoanisole and 4-$CF_3C_6H_4I$, respectively (Figure 4.7).

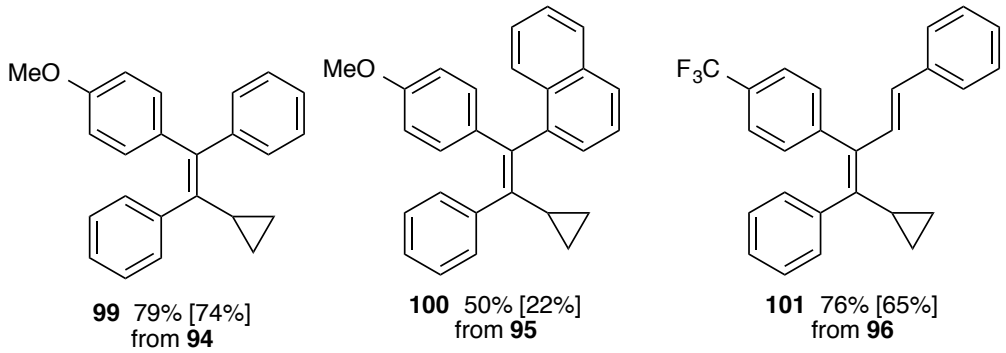
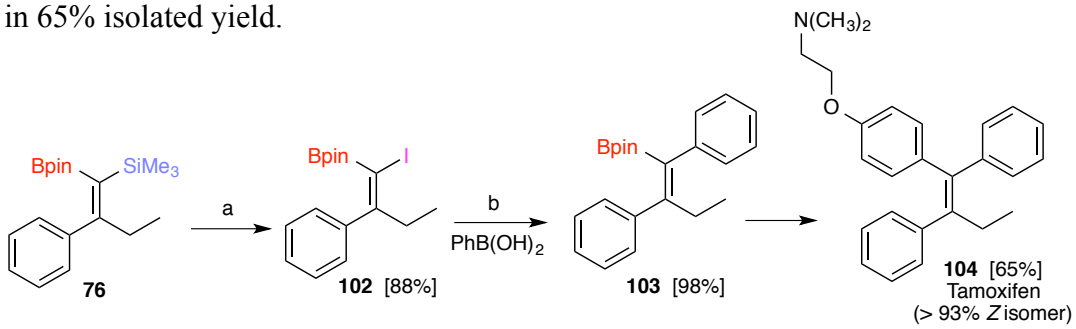


Fig. 4.7 Synthesis of tretrasubstituted alkenes via *gem*-silaborated products.

Taking into consideration the success on the synthesis of the tetrasubstituted alkenes with full guarantee of the stereocontrol, we planned to apply it to the synthesis of Tamoxifen through the *gem*-silaborated compound **76**.

As it can be seen in the scheme 4.10, the iododesilylation of **76** afforded compound **102** in 88% of isolated yield, which was further selectively submitted to cross coupling with $PhB(OH)_2$ to form **103** in very high yield (98%). The last step concerns to the second cross coupling leading to the desired product Tamoxifen **104** in 65% isolated yield.



Scheme 4.10 Synthesis of Tamoxifen via *gem*-silaborated product **15**. [a]$AgNO_3$, I_2, 0ºC, 30 min; [b]$Pd(PPh_3)_4$, $PhB(OH)_2$, TBAB, K_2CO_3, toluene, 90 ºC, 12h; [c]$Pd(PPh_3)_4$, RI, KOH, 1,4-dioxane, 90 ºC, 16h.

This modular stereoselective synthesis constitutes one of the most step- and cost-economic routes to this antagonist prodrug in all stages of estrogen-receptor-positive breast cancer.[17]

4.4 Conclusions

We conclude that $HC(Bpin)_2(SiMe_3)$ **62** represents a new olefination reagent that can be efficiently prepared antagonist *via* insertion of (trimethylsilyl)diazomethane into B_2pin_2. The straightforward access to *gem*-silaborated products opens the door to the modular synthesis of all-carbon tetrasubstituted alkenes *via* silicon or boron-based selective transformations. This novel protocol opens the door to the stereoselective preparation of tetrasubstituted olefins, exemplified here by the synthesis of Tamoxifen.

4.5 Experimental part

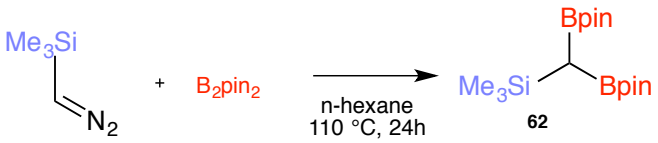
4.5.1 General Information *Solvents and reagents*: Solvents and reagents were obtained from commercial suppliers and dried and/or purified (if needed) by standard procedures, as specified in "Purification of Laboratory Chemicals".[1] Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl. (Trimethylsilyl)diazomethane solution 2.0 M in hexanes, lithium 2,2,6,6-tetramethylpiperidide as well as the carbonyl compounds, aryl halides and/or boronic acids employed were purchased from Sigma-Aldrich Inc. Bis(pinacolato)diboron was purchased from Ally Chem and used without further purification. All reactions were conducted in oven and flame-dried glassware under an inert atmosphere of argon, using Schlenk-type techniques. *Flash chromatography* was performed on standard silica gel (Merck Kieselgel 60 F254 400-630 mesh). *Thin layer chromatography* was performed on Merck Kieselgel 60 F254 which was developed using standard visualizing agents: UV fluorescence (254 and 366 nm) or potassium permanganate. *NMR spectr*a were recorded at a Varian Goku 400 or a Varian Mercury 400 spectrometer. ^{1}H NMR and ^{13}C{^{1}H} NMR chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: 7.26 ppm (^{1} H)) and ($CDCl_3$: 77.16 ppm (^{13}C). ^{11}B{^{1}H} NMR chemical shifts (δ) are reported in ppm relative to $(CH_3)_2O\cdots BF_3$. ^{29}Si{^{1}H} NMR chemical shifts (δ) are reported in ppm relative to $(CH_3)_4Si$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptuplet, br = broad, m = multiplet), coupling constants (Hz) and integration. *High resolution mass spectra (HRMS)* were recorded using a 6210 Time of Flight (TOF) mass spectrometer from Agilent Technologies (Waldbronn, Germany) with an ESI interface and it was performed at the Servei de Recursos Científics i Tècnics (Universitat Rovira I Virgili, Tarragona) or using a BIOTOF

[1] Perrin D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, Pergamon Press, 1988, 3rd Ed.

II Time of Flight (TOF) mass spectrometer from Bruker with an APCI interface or EI interface and it was performed at the Unidade de Espectrometría de Masas e Proteómica (Universidade de Santiago de Compostela, Santiago de Compostela). GC-MS analyses were performed on a HP6890 gas chromatograph and an Agilent Technologies 5973 Mass selective detector (Waldbronn, Germany) equipped with an achiral capillary column HP-5 (30m, 0.25mm i. d., 0.25µm thickness) using He as the carrier gas.

4.4.2 Experimental procedures and spectral data

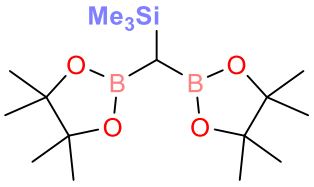
I.- General Procedure A: Insertion of (trimethylsilyl)diazomethane into pinB-Bpin.



In the glove-box, an oven-dried resealable Teflon screw-cap Schlenk reaction flask equipped with a magnetic stir bar was charged with 4 mmol (1 equiv.) of bis(pinacolato)diboron. Then, 2 equiv. (8 mmol) of a 2.0 M solution in hexanes of (trimethylsilyl)diazomethane were added dropwise. After stirring the mixture in the glove-box for 5 min the Schlenk flask was sealed and heated at 110 °C for 24 h while constantly stirring. The reaction was cooled at room temperature, the solvent was gently concentrated on a rotary evaporator and the resulting crude purified by silica gel flash chromatography to afford the 1,1 diborylated product.

Spectral data of 62

(Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane

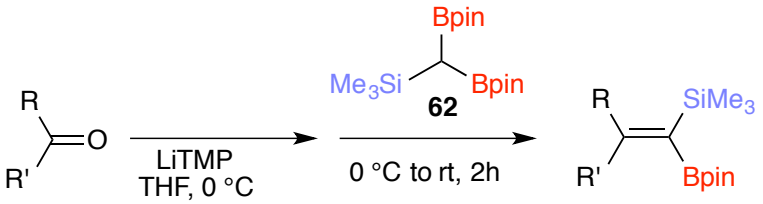


Flash column chromatography (hexane: ethyl acetate = 40:1) yielded **62** (87 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 12H), 1.19 (s, 12H), 0.30 (s, 1H), 0.10 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 82.8, 25.1, 24.6, 0.6. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 33.2. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ 2.0.

HRMS (EI) for $C_{15}H_{31}B_2O_4Si$ $[M\text{-}CH_3]^+$: calculated: 325.2178, found: 325.2173.

II.- Gem-silylborylation of ketones: General procedure B:



An oven dried resealable Schlenk tube equipped with a stirring bar was charged with compound **62** (0.1 mmol, 1 equiv.) and THF (0.2 mL) under Argon. The mixture was then cooled to 0 °C and lithium 2,2,6,6-tetramethylpiperidide (0.12 mmol, 1.2 equiv., 0.3 mL of a 0.4 M solution in THF) was added dropwise. After 5 min the ketone (0.15 mmol, 1.5 equiv.) was added and the reaction was allowed to warm up to r.t. Reaction mixture was analysed by TLC. After substrate completion (typically 2 h) the crude was filtered through a small pad of silica gel followed by a copious washing with diethyl ether. The solvent was gently concentrated at the rotary evaporator and the NMR yield was calculated through

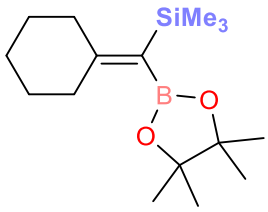
comparison to an internal standard (naphthalene). Purification by flash chromatography on silica gel afforded the desired product.

III.- Gem-silylborylation of ketones: General procedure C:

An oven dried resealable Schlenk tube equipped with a stirring bar was charged with compound **62** (0.18 mmol, 1.2 equiv.) and THF (0.2 mL) under Argon. The mixture was then cooled to 0 °C and lithium 2,2,6,6-tetramethylpiperidide (0.21 mmol, 1.4 equiv., 0.52 mL of a 0.4 M solution in THF) was added dropwise. After 5 min the ketone (0.15 mmol, 1.0 equiv.) was added and the reaction was allowed to warm up to r.t. Reaction mixture was analysed by TLC. After substrate completion (typically 2 h) the crude was filtered through a small pad of silica gel followed by a copious washing with diethyl ether. The solvent was gently concentrated at the rotary evaporator and the NMR yield was calculated through comparison to an internal standard (naphthalene). Purification by flash chromatography on silica gel afforded the desired product.

Spectral data of gem-bismetalated alkenes

(cyclohexylidene(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane



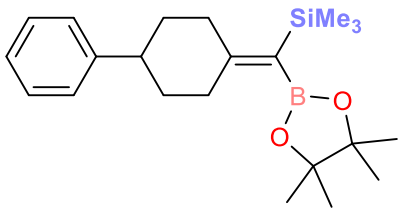
Flash column chromatography (hexane: ethyl acetate = 60:1) yielded **63** (95 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34–2.18 (m, 4H), 1.70–1.47 (m, 6H). 1.28 (s, 12H), 0.13 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 166.7, 110.1, 83.2,

39.5, 37.4, 29.0, 28.7, 26.4, 25.3, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.8. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.1.

HRMS (EI) for $C_{16}H_{31}BO_2Si$ $[M]^+$: calculated: 294.2186, found: 294.2187.

Trimethyl((4-phenylcyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane

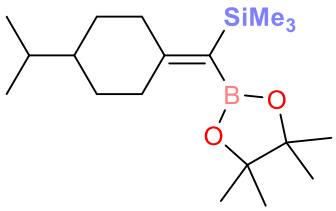


Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **64** (83 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–6.95 (m, 5H), 2.82–2.66 (m, 2H), 2.63–2.52 (m, 1H), 2.31 (td, *J* = 13.1, 4.1 Hz, 1H), 2.19 (td, *J* = 13.4, 4.2 Hz, 1H), 2.06–1.95 (m, 2H), 1.72 (td, *J* = 12.8, 3.6 Hz, 1H), 1.59 (td, *J* = 12.8, 3.6 Hz, 1H), 1.31 (s, 6H), 1.31 (s, 6H), 0.18 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 165.0, 146.7, 128.5, 127.0, 126.1, 83.3, 44.3, 39.1, 36.9, 36.0, 36.0, 25.5, 25.3, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 33.9. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -10.8.

HRMS (ESI) for $C_{22}H_{35}BNaO_2Si$ $[M+Na]^+$: calculated: 369.2536, found: 369.2544.

((4-isopropylcyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane

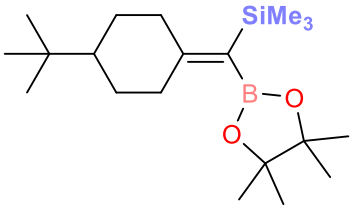


Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **65** (87 %).

^{1}H NMR (400 MHz, $CDCl_3$,) δ 2.63-2.54 (m,1 H), 2.48-2.39 (m, 1H), 2.11 (td, *J* = 13.0, 4.3 Hz, 1H), 1.99 (td, *J* = 13.2, 4.2 Hz, 1H), 1.85-1.74 (m, 2H), 1.49-1.37 (m, 1H), 1.29 (s, 12H), 1.23-1.11 (m, 3H), 0.84 (d, *J* = 6.8 Hz, 6H), 0.14 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$,) δ 166.7, 83.2, 43.8, 38.9, 36.7, 32.5, 31.8, 31.5, 25.4, 25.3, 20.1, 20.1, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 33.4. **^{29}Si NMR** (79.5 MHz, $CDCl_3$,) δ -11.1.

HRMS (ESI) for $C_{19}H_{37}BNaO_2Si$ $[M+Na]^+$: calculated: 359.2552, found: 359.2552.

((4-(tert-butyl)cyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane

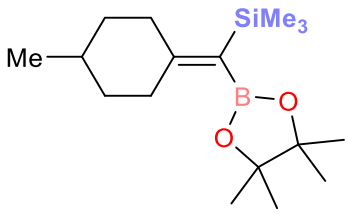


Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **66** (82 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.55 (m, 1H), 2.53-2.40 (m, 1H), 2.19-2.05 (m, 1H), 1.98 (td, *J* = 13.1, 4.2 Hz, 1H), 1.92-1.78 (m, 2H), 1.29 (s, 12H), 1.24-1.10 (m, 3H), 0.84 (s, 9H), 0.14 (s, 9H).**^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 166.6, 83.23, 48.0, 39.1, 37.0, 32.5, 29.6, 29.1, 27.7, 25.4, 25.3, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 33.6. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.1.

HRMS (ESI) for $C_{20}H_{39}BNaO_2Si$ $[M+Na]^+$: calculated: 373.2709, found: 373.2708

Trimethyl((4-methylcyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane

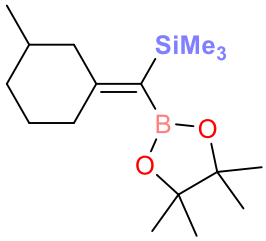


Flash column chromatography (hexane: ethyl acetate = 40:1) yielded **67** (88 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59-2.47 (m, 1H), 2.45-2.33 (m, 1H), 2.13 (td, *J* = 13.1, 4.4 Hz, 1H), 2.02 (td, *J* = 13.1, 4.3 Hz, 1H), 1.84-1.71 (m, 2H), 1.66-1.50 (m, 1H), 1.28 (d, *J* = 1.4 Hz, 12H) 1.19-1.01 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.13 (m, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 166.4, 83.2, 38.7, 37.1, 36.8, 36.6, 32.4, 25.4, 25.3, 21.9, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 33.3. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.1.

HRMS (EI) for $C_{17}H_{33}BO_2Si$ $[M]^+$: calculated: 308.2343, found: 308.2358.

Trimethyl((3-methylcyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane

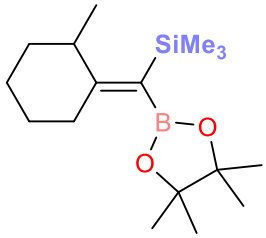


Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **68/68'** (90 %; 55:45).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55–2.42 (m, 0.55 x 1H **68** + 0.45 x 1H **68'**), 2.42–2.31 (m, 0.55 x 1H **68** + 0.45 x 1H **68'**), 2.07–1.88 (m, 0.55 x 1H **68** + 0.45 x 1H **68'**), 1.84–1.64 (m, 0.55 x 3H **68** + 0.45 x 3H **68'**), 1.62–1.32 (m, 0.55 x 2H **68** + 0.45 x 2H **68'**), 1.31–1.23 (m, 0.55 x 12H **68** + 0.45 x 12H **68'**), 1.15–0.97 (m, 0.55 x 1H **68** + 0.45 x 1H **68'**), 0.94–0.83 (m, 0.55 x 3H **68** + 0.45 x 3H **68'**), 0.15–0.10 (m, 0.55 x 9H **68** + 0.45 x 9H **68'**).**^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 166.1, 166.0, 83.2, 47.8, 45.7, 38.8, 36.7, 35.2, 35.0, 34.9, 34.6, 27.9, 27.4, 25.4, 25.4, 25.2, 25.2, 22.7, 22.4, 1.2, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.6 (0.55 x 1B **68** + 0.45 x 1B **68'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.0, -11.1.

HRMS (EI) for $C_{17}H_{33}BO_2Si$ $[M]^+$: calculated: 308.2343, found: 308.2345.

Trimethyl((2-methylcyclohexylidene)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane



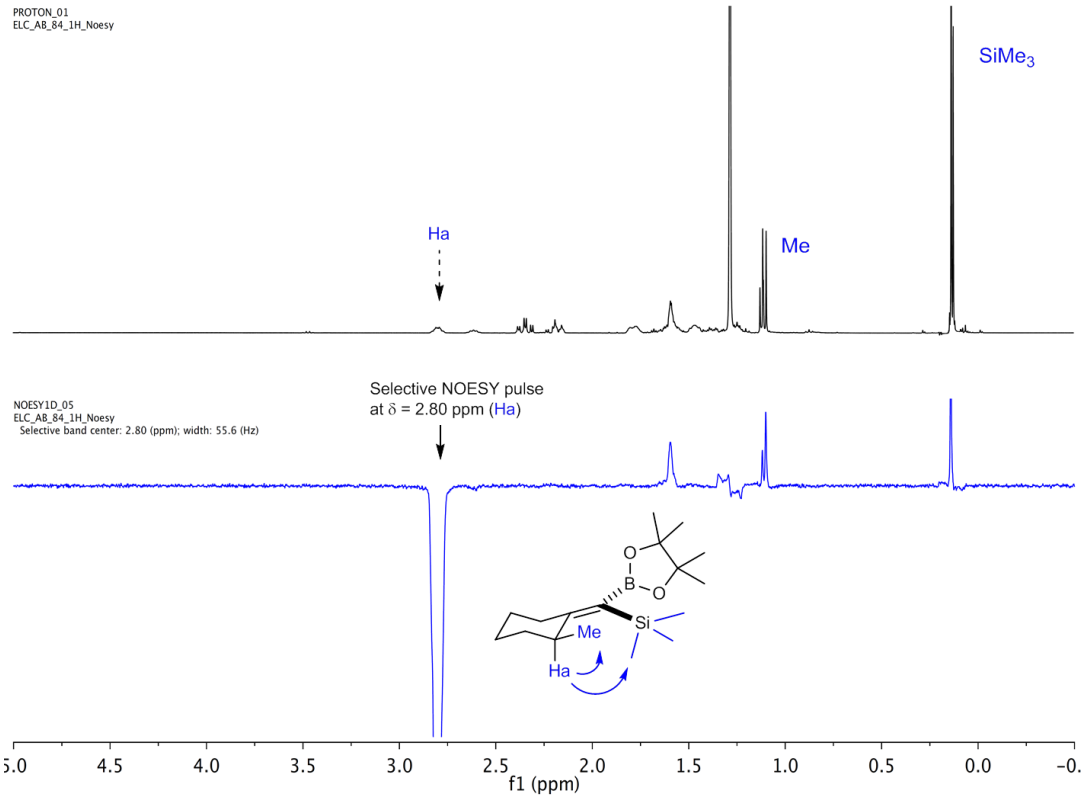
Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **69** (70 %; *Z*/*E* 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87–2.74 (m, 0.7x 1H **69**), 2.68–2.54 (m, 0.3 x 1H **69'**), 2.34 (td, *J* = 13.5, 4.6 Hz, 0.7 x 1H **69** + 0.3 x 1H **69'**), 2.25–2.13 (m, 0.7 x 1H **69** + 0.3 x 1H **69'**), 1.84-1.73 (m, 0.7 x 1H **69** + 0.3 x 1H **69'**), 1.66–1.51 (m, 0.7 x 3H **69** + 0.3 x 3H **69'**), 1.51–1.33 (m, 0.7 x 2H **69** + 0.3 x 2H **69'**), 1.28 (m, 0.7 x 12H **69** + 0.3 x 12H **69'**), 1.11 (dd, *J* = 7.1, 5.6 Hz, 0.7 x 3H **69** + 0.3 x 3H **69'**), 0.14 (s, 6H **69**), 0.13 (s, 3H **69'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 170.2, 169.7, 83.1, 83.1, 41.4, 38.9, 34.1, 34.1, 33.8, 32.1, 29.2, 28.4, 25.4, 25.3, 25.2, 20.4, 20.3, 19.3, 18.4, 1.2, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.6 (0.7 x 1B **69** +0.3 x 1B **69'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.4, -11.9.

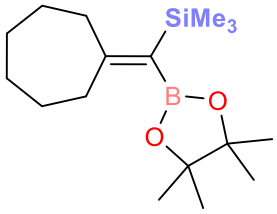
HRMS (EI) for $C_{17}H_{33}BO_2Si$ $[M]^+$: calculated: 308.2343, found: 308.2354.

Polarization transfer NMR experiments to determine configuration of compound 69.

Based on the 1D selective NOE NMR experiments the configuration of isomer **69** was confirmed.



(cycloheptylidene(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane

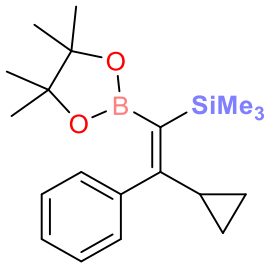


Flash column chromatography (hexane: ethyl acetate = 80:1) yielded **70** (56 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49–2.33 (m, 4H), 1.67–1.43 (m, 8H), 1.29 (s, 12H), 0.14 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 168.1, 83.1, 39.0, 38.2, 30.1, 28.7, 28.6, 27.6, 25.3, 24.9, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.8. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.5.

HRMS (APCI) for $C_{17}H_{33}BNaO_2Si$ $[M+Na]^+$: calculated: 331.2238, found: 331.2238.

(2-cyclopropyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)trimethylsilane



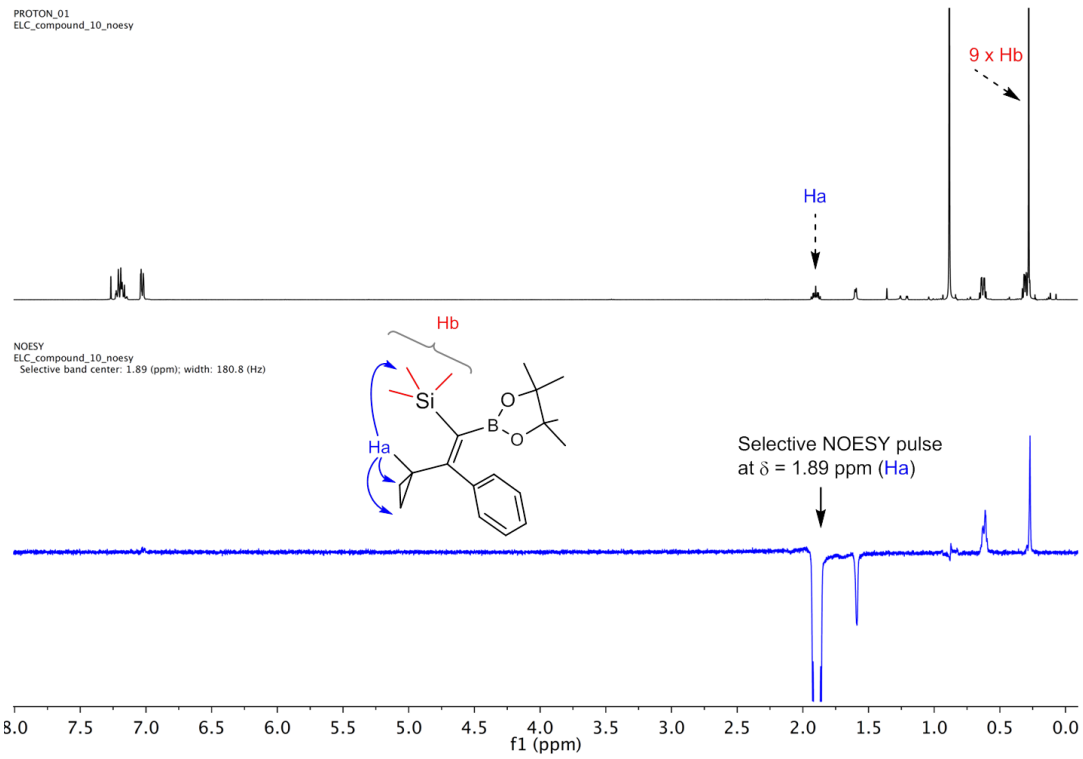
Flash column chromatography (hexane: ethyl acetate = 80:1) yielded **71** (89 %; ≥ 95 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (m, 3H), 7.05–6.97 (m, 2H), 1.89 (tt, *J* = 8.3, 5.2 Hz, 1H), 0.87 (s, 12H), 0.65–0.58 (m, 2H), 0.32–0.27 (m, 2H), 0.27 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 165.4, 141.4, 129.3, 127.3, 126.6, 83.0, 24.9, 19.1, 5.8, 1.1. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 31.8. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -10.1.

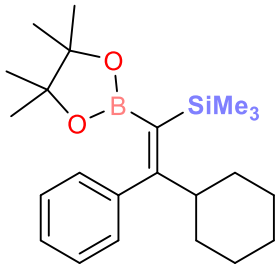
HRMS (EI) for $C_{20}H_{31}BO_2Si$ $[M]^+$: calculated: 342.2186, found: 342.2177.

Polarization transfer NMR experiments to determine configuration of compound 71.

Based on the 1D selective NOE NMR experiments the configuration of isomer **71** was confirmed.



(2-cyclohexyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)trimethylsilane

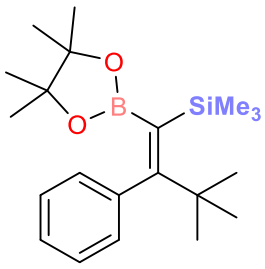


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **72** (86 %; 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 3H), 7.07-7.02 (m,2H) 2.58 (tt, *J* = 11.8, 2.7 Hz, 1H), 1.75–1.63 (m, *J* = 11.0 Hz, 3H), 1.61–1.51 (m, 2H), 1.34–1.17 (m, *J* = 16.4, 5.0 Hz, 2H), 1.16–0.91 (m, 3H), 0.87 (s, 12H), 0.23 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 170.2, 143.3, 129.2, 127.1, 126.2, 83.0, 48.8, 31.4, 26.3, 25.8, 24.9, 1.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.0. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.1.

HRMS (EI) for $C_{23}H_{37}BO_2Si$ $[M]^+$: calculated: 384.2656, found: 384.2660.

(3,3-dimethyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)trimethylsilane



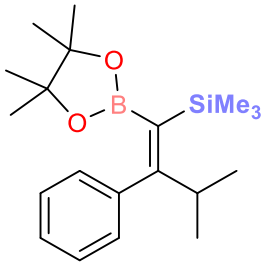
Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **73** (52 %; 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.13 (m, 3H), 7.09-7.03 (m, 2H), 1.09 (s, 9H), 0.87 (s, 12H), 0.30 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 172.9, 146.2, 129.0, 127.2, 126.0, 83.2, 39.1, 31.8, 26.3, 25.9, 25.7, 24.9, 3.4. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 31.4. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -13.3.

HRMS (EI) for $C_{20}H_{32}BO_2Si$ $[M\text{-}CH_3]^+$: calculated: 343.2265, found:

343.2265.

Trimethyl(3-methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)silane

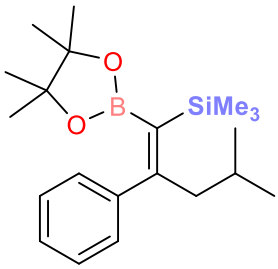


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **74** (67 %; 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.16 (m, 3H), 7.09–7.04 (m, 2H), 3.02–2.91 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 6H), 0.87 (s, 12H), 0.23 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 170.4, 142.3, 129.5, 127.1, 126.3, 83.0, 37.6, 24.9, 21.3, 1.1. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 31.8. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.2.

HRMS (EI) for $C_{20}H_{33}BO_2Si$ $[M]^+$: calculated: 344.2343, found: 344.2355.

Trimethyl(4-methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-1-yl)silane

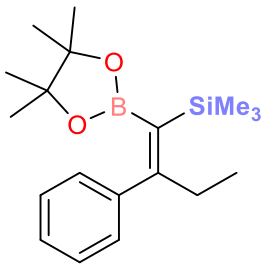


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **75/75'** (60 %; 91:9 ratio of *E*/*Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.16 (m, 0.91 x 5H **75** + 0.09 x 5H **75'**), 2.46 (d, *J* = 7.3 Hz, 0.91 x 2H **75**), 2.42 (*J* = 7.3 Hz, 0.09 x 2H **75'**) 1.46–1.36 (m, 0.91 x 1H **75** + 0.09 x 1H **75'**), 1.35 (s, 0.09 x 12H **75'**) 0.98 (s, 0.91 x 12H **75**), 0.84 (d, *J* = 6.6 Hz, 0.09 x 6H **75'**), 0.80 (d, J = 6.6 Hz, 0.91 x 6H **75**) 0.24 (s, 0.91 x 9H **75**), -0.21 (s, 0.09 x 9H **75'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 164.6, 146.0, 128.0, 127.8, 127.7, 126.7, 83.1, 48.2, 26.5, 25.5, 25.2, 22.5, 22.4, 1.5. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.2 (0.91 x 1B **75** + 0.09 x 1B **75'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.3 -10.4.

HRMS (EI) for $C_{21}H_{35}BO_2Si$ $[M]^+$: calculated: 358.2499, found: 358.2510.

Trimethyl(2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)silane

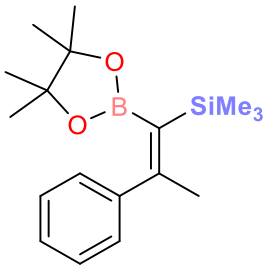


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **76/76'** (40 %; 90:10 ratio of *E*/*Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 0.9 x 5H **76** + 0.1 x 5H **76'**), 2.57–2.50 (m, 0.9 x 2H **76** + 0.1 x 2H **76'**), 1.35 (s, 0.1 x 12H **76'**) 0.96 (s, 0.9 x 12H **76**), 0.86 (t, *J* = 7.5 Hz, 0.9 x 3H **76** + 0.1 x 3H **76'**), 0.23 (s, 0.9 x 9H **76**), -0.22 (s, 0.1 x 9H **76'**) . **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 167.1, 145.7, 128.2, 128.0, 127.7, 126.7, 83.1, 33.0, 29.8, 25.3, 25.1, 13.2, 1.1, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.0 (0.9 x 1B **76** + 0.1 x 1B **76'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -10.3.

HRMS (EI) for $C_{19}H_{31}BO_2Si$ $[M]^+$: calculated: 330.2186, found: 330.2181.

Trimethyl(2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)silane

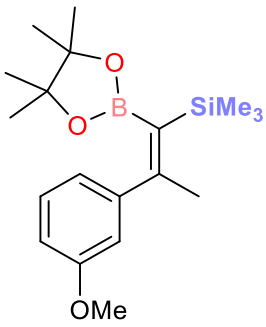


Flash column chromatography (hexane: ethyl acetate = 50:1) yielded **77/77'** (40 %; 87:13 ratio of *E*/*Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 0.87 x 5H **77** + 0.13 x 5H **77'**), 2.22 (s, 0.13 x 3H **77'**) 2.20 (s, 0.87 x 3H **77**), 1.35 (s, 0.13 x 12H **77'**), 1.00 (s, 0.87 x 12H **77**), 0.24 (s, 0.87 x 9H **77**), -0.21 (s, 0.13 x 9H **77'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 160.9, 148.0, 127.9, 127.3, 127.2, 126.9, 83.1, 26.5, 25.4, 25.1, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.4 (0.87 x 1B **77** + 0.13 x 1B **77'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.0, -9.5.

HRMS (EI) for $C_{18}H_{29}BO_2Si$ $[M]^+$: calculated: 316.2030, found: 316.2025.

2-(3-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)trimethylsilane

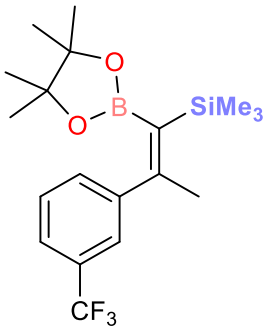


Flash column chromatography (hexane: ethyl acetate = 60:1) yielded **78/78'** (42 %; 89:11 ratio of *E/Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.9 Hz, 0.89 x 1H **78** + 0.11 x 1H **78'**), 6.86 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 0.89 x 1H **78** + 0.11 x 1H **78'**), 6.81 (dd, *J* = 2.4, 1.6 Hz, 0.89 x 1H **78** + 0.11 x 1H **78'**), 6.75 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 0.89 x 1H **78** + 0.11 x 1H **78'**), 3.80 (s, 0.89 x 3H **78** + 0.11 x 3H **78'**), 2.19 (s, 0.89 x 3H **78** + 0.11 x 3H **78'**), 1.31 (s, 0.11 x 12H **78'**) 1.01 (s, 0.89 x 12H **78**), 0.24 (s, 0.89 x 9H **78**), -0.18 (s, 0.11 x 9H **78'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 160.8, 159.2, 149.4, 129.2, 129.0, 119.6, 112.9, 112.3, 83.1, 55.3, 29.8, 26.3, 25.4, 25.1, 25.0, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.0 (0.89 x 1B **78** + 0.11 x 1B **78'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.5.

HRMS (EI) for $C_{19}H_{31}BO_2Si$ $[M]^+$: calculated: 346.2136, found: 346.2134.

Trimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(3-(trifluoromethyl)phenyl)prop-1-en-1-yl)silane

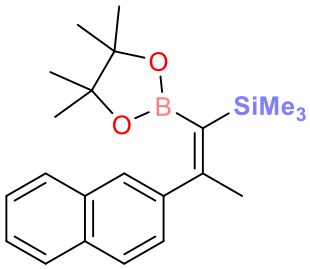


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **79**/**79'** (70 %; 87:13 ratio of *E*/*Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.31 (m, 0.87 x 4H **79** + 0.13 x 4H **79'**), 2.22 (s, 0.13 x 3H **79'**) 2.19 (s, 0.87 x 3H **79**), 1.35 (s, 0.13 x 12H **79'**) 0.96 (s, 0.87 x 12H **79**), 0.25 (s, 0.87 x 9H **79**), -0.22 (s, 0.13 x 9H **79'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 159.2, 159.0, 148.4, 147.8, 130.6, 130.5, 130.4, 130.1, 128.5, 128.4, 125.6, 124.4, 124.4, 124.2, 124.2, 123.6, 123.6, 83.7, 83.3, 29.1, 26.5, 25.3, 24.9, 0.7. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.1 (0.87 x 1B **79** + 0.13 x 1B **79'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -8.7, -9.0.

HRMS (EI) for $C_{19}H_{28}BO_2F_3Si$ $[M]^+$: calculated: 384.1904, found: 384.1905.

Trimethyl(2-(naphthalen-2-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)silane

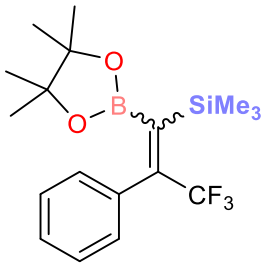


Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **80/80'** (50 %; 88:12 ratio of *E*/*Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.72 (m, 0.88 x 4H **80** + 0.12 x 4H **80'**), 7.48–7.39 (m, 0.88 x 3H **80** + 0.12 x 3H **80'**), 2.30-2.29 (m, 0.88 x 3H **80** + 0.12 x 3H **80'**), 1.38 (s, 0.12 x 12H **80'**) 0.88 (s, 0.88 x 12H **80**), 0.28 (s, 0.88 x 9H **80**), -0.21 (s, 0.12 x 9H **80'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 160.8, 145.6, 133.2, 132.5, 128.0, 127.8, 127.7, 127.5, 126.1, 126.0, 125.8, 125.7, 125.6, 125.6, 83.6, 83.1, 26.2, 25.4, 25.0, 1.0, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.6 (0.88 x 1B **80** + 0.12 x 1B **80'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.0, -9.4.

HRMS (EI) for $C_{22}H_{31}BO_2Si$ $[M]^+$: calculated: 366.2186, found: 366.2176.

Trimethyl(3,3,3-trifluoro-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)silane

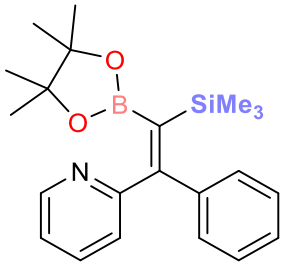


Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **81/81'** (91 %; 63:37 ratio of *Z*/*E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 0.63 x 5H **81** + 0.37 x 5H **81'**), 1.36 (s, 0.37 x 12H **81'**), 0.93 (s, 0.67 x 12H **81**), 0.27 (d, *J* = 1.1 Hz, 0.67 x 9H **81**), -0.15 (s, 0.37 x 9H **81'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 147.7, 147.4, 138.0, 136.8, 129.8, 129.6, 128.6, 128.3, 128.0, 127.9, 84.4, 84.1, 25.6, 25.2, 0.6, 0.5, 0.5, 0.5, 0.1. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 31.7 (0.63 x 1B **81** + 0.37 x 1B **81'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -5.1, -7.6.

HRMS (EI) for $C_{17}H_{23}BO_2F_3Si$ $[M]^+$: calculated: 355.1512, found: 355.1516.

2-(1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)vinyl)pyridine

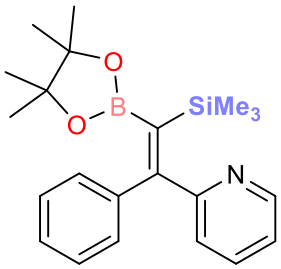


Flash column chromatography (hexane: ethyl acetate = 3:1) yielded **82** (63 % as a pure *E* isomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67–8.57 (m, 1H), 7.70 (td, *J* = 7.8, 1.5 Hz, 1H), 7.44–7.30 (m, 3H), 7.25–7.15 (m, 3H), 6.79 (d, *J* = 7.9 Hz, 1H), 1.44 (s, 12H), -0.05 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 157.2, 150.8, 142.4, 141.5, 139.3, 129.5, 128.4, 127.1, 121.6, 119.1, 81.9, 66.0, 29.8, 28.4, 24.9, 15.4, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 16.6. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -7.4.

HRMS (EI) $C_{22}H_{30}BNO_2Si$ $[M]^+$: calculated: 379.2139, found: 379.2142.

2-(1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)vinyl)pyridine

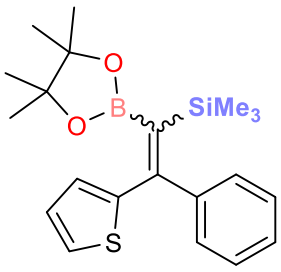


Flash column chromatography (hexane: ethyl acetate = 20:1) yielded **82'** (37 % as a pure *Z* isomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 11.8, 5.1, 4.3 Hz, 1H), 7.53 (td, *J* = 7.7, 1.8 Hz, 1H), 7.35–7.21 (m, 5H), 7.13 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 1.01 (s, 12H), 0.06 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 159.6, 148.0, 144.1, 136.0, 129.4, 127.9, 127.3, 123.5, 122.1, 83.4, 25.1, 1.9. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.6. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -11.7.

HRMS (EI) for $C_{22}H_{30}BNO_2Si$ $[M]^+$: calculated: 379.2139, found: 379.2140.

Trimethyl(2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(thiophen-2-yl)vinyl)silane



Flash column chromatography (hexane: ethyl acetate = 60:1) yielded **83/83'** (91 %; 65:35 isomeric ratio (*major isomer assigned by comparison of the relative position of Bpin and TMSi groups with the spectral data of isomers* **21** *and* **21'**)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 0.65 x 5.5H **83** + 0.35 x 5.5H **83'**), 7.19 (dd, *J* = 5.1, 1.2 Hz, 0.65 x 0.5H **83** + 0.35 x 0.5H **83'**), 7.11 (dd, *J* = 3.6, 1.2 Hz, 0.65 x 0.5H **83** + 0.35 x 0.5H **83'**), 6.97 (dd, *J* = 3.5, 1.2 Hz, 0.65 x 0.5H **83** + 0.35 x 0.5H **83'**), 6.92 (dd, *J* = 5.0, 3.5 Hz, 0.65 x 0.5H **83** + 0.35 x 0.5H **83'**), 6.88 (dd, *J* = 5.1, 3.6 Hz, 0.65 x 0.5H **83** + 0.35 x 0.5H **83'**), 1.25 (s, 0.65 x 12H **83**), 1.05 (s, 0.35 x 12H **83'**), 0.03 (d, *J* = 3.2 0.35 x 9H **83'**), -0.12 (s, 0.65 x 9H **83**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 155.7, 155.0, 149.3, 147.1, 146.1, 145.1, 128.9, 128.5, 127.9, 127.8, 127.6, 127.5, 127.1, 126.8, 126.3, 126.3, 126.3, 126.0, 83.8, 83.5, 25.5, 25.0, 0.9, 0.8. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.5 (0.65 x 1B **83** +0.35 x 1B **83'**). **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -7.5, -7.9.

HRMS (EI) for $C_{21}H_{29}BO_2SiS$ $[M]^+$: calculated: 384.1751, found: 384.1755.

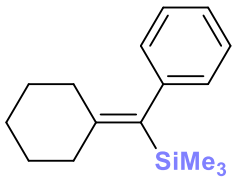
IV Derivatization of gem-bismetalated alkenes

IV. a. Suzuki-Miyaura cross-coupling with gem-silyl boronates: General procedure D:

An oven dried resealable Schlenk tube equipped with a stirring bar was charged with $Pd(PPh_3)_4$ (3 mol%) and 1,4-dioxane (0.7 mL). To this solution the corresponding *gem*-bismetalted alkene (1 equiv.), dissolved in 0.6 mL of 1,4-dioxane, aryl iodide (3 equiv.) and a 3M KOH solution (6 equiv.) were added in sequence and the reaction was heated up at 90 °C overnight (typically 16 h). After completion (by TLC), the mixture was cooled to room temperature diluted with DCM. The mixture was filtered through a small pad of Celite® and anhydrous $MgSO_4$. Afterwards the solvent was concentrated at the rotary evaporator and the NMR yield calculated through internal standard (1,4-dinitrobenzene). The resulting crude product was purified by column chromatography (silica gel) to give a coupled compound.

Spectral data of trisubstituted vinyl silanes

(cyclohexylidene(phenyl)methyl)trimethylsilane

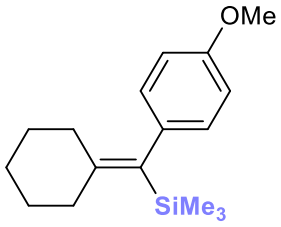


Flash column chromatography (hexane 100 %) yielded **84** (65 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H), 7.15–7.09 (m, 1H), 6.89–6.83 (m, 2H), 2.41–2.34 (m, 2H), 1.94–1.88 (m, 2H), 1.71–1.62 (m, 2H), 1.61–1.55 (m, 2H), 1.49-1.40 (m, 2H), 0.02 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 153.1, 145.5, 134.7, 128. 127.8, 124.7, 35.4, 33.4, 29.0, 28.9, 26.8, 0.9. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -8.7.

HRMS (EI) for $C_{16}H_{24}Si$ $[M]^+$: calculated: 244.1647, found: 244.1638.

(cyclohexylidene(4-methoxyphenyl)methyl)trimethylsilane

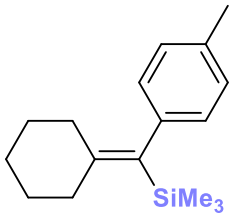


Flash column chromatography (hexane 100 %) yielded **85** (55 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90–6.66 (m, 4H), 3.79 (s, 3H), 2.39–2.30 (m, 2H), 1.95–1.86 (m, 2H), 1.69–1.51 (m, 4H), 1.48–1.37 (m, 2H), 0.02 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 156.9, 153.6, 137.8, 134.0, 129.1, 113.2, 55.2, 35.4, 33.3, 29.0, 28.9, 26.8, 1.0. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -8.8.

HRMS (EI) for $C_{17}H_{26}OSi$ $[M]^+$: calculated: 274.1753, found: 274.1754.

(cyclohexylidene(p-tolyl)methyl)trimethylsilane

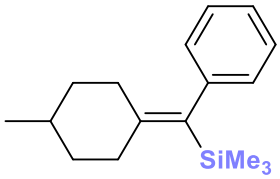


Flash column chromatography (hexane 100 %) yielded **86** (79 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (apparent d, *J* = 8.0 Hz, 2H), 6.75 (apparent d, *J* = 8.0 Hz, 2H), 2.39-2.33 (m, 2H), 2.32 (s, 3H), 1.94-1.87 (m, 2H), 1.69-1.61 (m, 2H), 1.60–1.53 (m, 2H), 1.49–1.40 (m, 2H), 0.02 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 153.2, 142.4, 134.5, 133.9, 128.6, 128.1, 35.4, 33.3, 29.1, 28.9, 26.8, 21.2, 1.0. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.0.

HRMS (EI) for $C_{17}H_{26}Si$ $[M]^+$: calculated: 258.1804, found: 258.1801.

Trimethyl((4-methylcyclohexylidene)(phenyl)methyl)silane

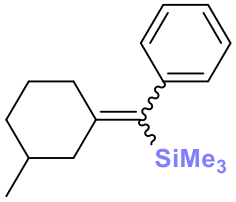


Flash column chromatography (hexane 100 %) yielded **87** (91 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.21 (m, 2H), 7.16-7.08 (m, 1H), 6.91-6.81 (m, 2H), 2.66 (ddd, *J* = 13.3, 5.9, 3.5 Hz, 1H), 2.22–2.05 (m, 2H), 1.91–1.81 (m, 1H), 1.71–1.55 (m, 3H), 1.18–1.05 (m, 1H), 0.98–0.84 (m, 4H), 0.02 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 152.8, 145.6, 134.9, 128.3, 128.2, 127.9, 124.7, 37.2, 37.1, 34.6, 32.7, 32.6, 22.1, 0.1. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -8.9.

HRMS (EI) for $C_{17}H_{26}Si$ $[M]^+$: calculated: 258.1804, found: 258.1806.

Trimethyl((3-methylcyclohexylidene)(phenyl)methyl)silane

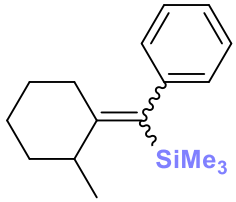


Flash column chromatography (hexane 100 %) yielded **88/88'** (80 %; diastereomeric ratio 55:45).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 0.55 x 2H **88** + 0.45 x 2H **88'**), 7.12 (m, 0.55 x 1H **88** + 0.45 x 1H **88'**), 6.90-6.82 (m, 0.55 x 2H **88** + 0.45 x 2H **88'**), 2.66-2.54 (m, 0.55 x 1H **88** + 0.45 x 1H **88'**), 2.14 (m, 0.55 x 1H **88** + 0.45 x 1H **88'**), 2.08-0.73 (m, 0.55 x 10H **88** + 0.45 x 10H **88'**), 0.02 (s, 0.55 x 9H **88** + 0.45 x 9H **88'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 152.7, 152.3, 145.6, 145.6, 135.5, 134.8, 128.3, 128.2, 127.9, 127.9, 124.7, 43.7, 41.4, 35.4, 35.3, 35.1, 34.9, 34.8, 32.8, 27.8, 27.7, 22.7, 22.4, 1.0, 1.0. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -8.8.

HRMS (EI) for $C_{17}H_{26}Si$ $[M]^+$: calculated: 258.1804, found: 258.1813.

Trimethyl((2-methylcyclohexylidene)(phenyl)methyl)silane

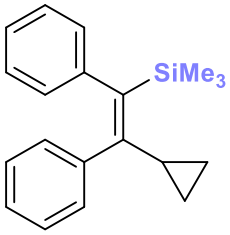


Flash column chromatography (hexane 100 %) yielded **89/89'** (50 %; diastereomeric ratio 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 0.70 x 2H **89** +0.30 x 2H **89'**), 7.15-7.08 (m, 0.70 x 1H **89** +0.30 x 1H **89'**), 6.90-6.78 (m, 0.70 x 2H **89** +0.30 x 2H **89'**), 2.98-2.86 (m, 0.70 x 1H **89**), 2.51-2.41 (m, 0.30 x 1H **89'**), 2.28 (td, *J* = 13.7, 4.3 Hz, 0.30 x 1H **89'**), 2.02-1.95 (m, 0.70 x 1H **89**), 1.92-1.87 (m, 0.30 x 1H **89'**), 1.82 (td, *J* = 13.5, 4.2 Hz, 0.70 x 1H **89**), 1.72-1.31 (m, 0.70 x 5H **89** + 0.30 x 5H **89'**), 1.22-1.09 (m, 0.70 x 4H **89**), 0.99-0.79 (m, 0.30 x 4H **89'**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 157.1, 156.5, 145.7, 134.6, 134.5, 128.3, 128.2, 128.0, 127.9, 127.9, 127.9, 124.7, 36.7, 34.1, 34.0, 33.9, 30.1, 29.1, 29.0, 27.8, 20.8, 20.8, 18.8, 18.6, 0.9, 0.9. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -9.0, -9.4.

HRMS (EI) for $C_{17}H_{26}Si$ $[M]^+$: calculated: 258.1804, found: 258.1803.

(2-cyclopropyl-1,2-diphenylvinyl)trimethylsilane

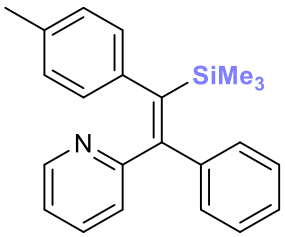


Flash column chromatography (hexane 100 %) yielded **90** (60 %; 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–6.91 (m, 5H), 6.89–6.82 (m, 1H), 6.80–6.74 (m, 2H), 6.72–6.66 (m, 2H), 2.03 (tt, *J* = 8.3, 5.2 Hz, 1H), 0.72–0.64 (m, 2H), 0.37–0.28 (m, 2H), 0.17 (s, *J* = 1.3 Hz, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 154.4, 145.1, 140.3, 139.0, 129.8, 128.8, 127.1, 126.8, 125.6, 124.2, 17.4, 5.6, 0.9. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -7.3.

HRMS (EI) for $C_{20}H_{24}Si$ $[M]^+$: calculated: 292.1647, found: 292.1647.

2-(1-phenyl-2-(p-tolyl)-2-(trimethylsilyl)vinyl)pyridine

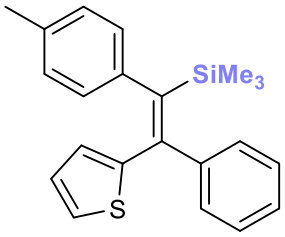


Flash column chromatography (hexane: ethyl acetate = 40:1) yielded **91** (43 %; 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 7.47 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.39–7.25 (m, 4H), 6.95–6.82 (m, 6H), 2.22 (s, 3H), -0.18 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 161.2, 153.0, 148.6, 145.9, 142.7, 140.3, 135.3, 134.4, 129.4, 128.7, 128.1, 127.9, 127.3, 124.4, 120.7, 21.0, 0.3. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -5.6.

HRMS (EI) for $C_{23}H_{25}NSi$ $[M]^+$: calculated: 343.1756, found: 343.1750.

Trimethyl(2-phenyl-2-(thiophen-2-yl)-1-(p-tolyl)vinyl)silane



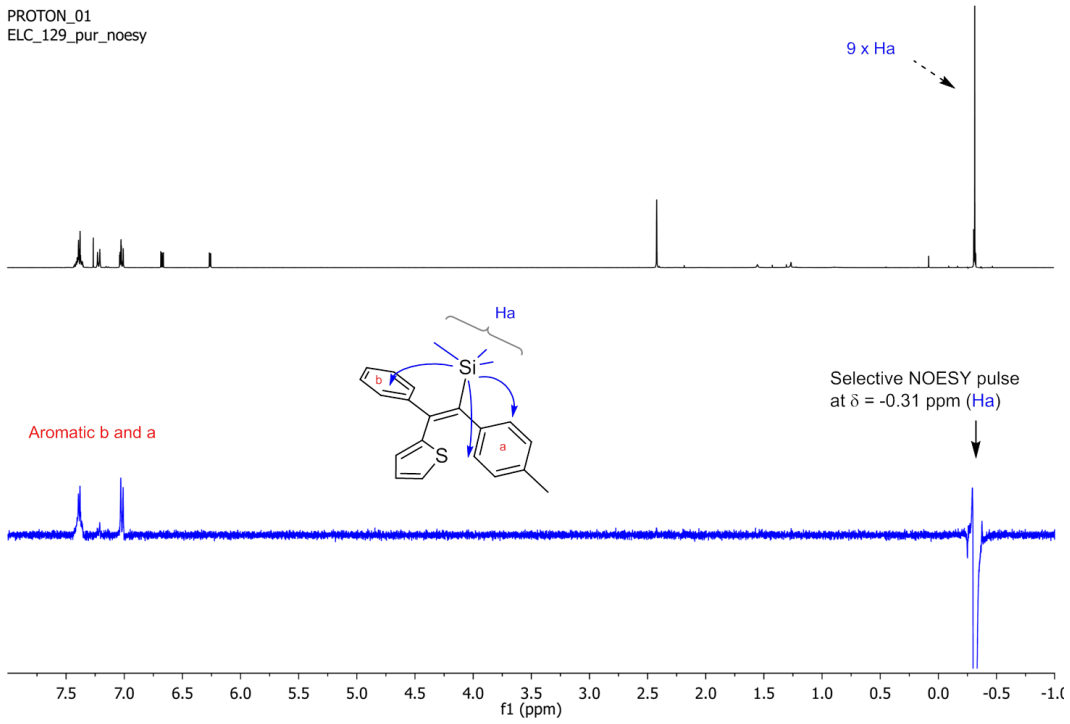
Flash column chromatography (hexane 100 %) yielded only the major isomer **92** as a pure product (62 %; isolated from the diastereomeric ratio 65:35).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5H), 7.21 (dd, *J* = 8.3, 0.6 Hz, 2H), 7.05–6.98 (m, 3H), 6.67 (dd, *J* = 5.1, 3.8 Hz, 1H), 6.26 (dd, *J* = 3.8, 1.2 Hz, 1H), 2.42 (s, 3H), -0.32 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 145.6, 144.4, 143.3, 143.0, 140.7, 136.1, 130.5, 129.8, 129.7, 128.7, 128.1, 127.2, 127.3, 125.3, 21.5, 0.1. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -6.0.

HRMS (EI) for $C_{22}H_{24}SSi$ $[M]^+$: calculated: 348.1368, found: 348.1377.

Polarization transfer NMR experiments to determine configuration of compound 92.

Based on the 1D selective NOE NMR experiments the configuration of isomer **92** was confirmed.



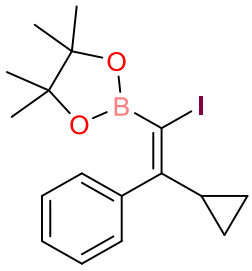
IV. b. Iododesilylation: General procedure E:

An oven dried resealable Schlenk tube equipped with a stirring bar was charged with a solution of *gem*-silyl boronate (0.3 mmol; 1.0 equiv.) in anhydrous methanol (5,22 mL). The solution was cooled at 0 ºC and 0.45 mmol (1.5 equiv. of $AgNO_3$ were added. The mixture was stirred for 10 min to ensure complete dissolution. Then, Iodine (0.36 mmol; 1.2 equiv.) was added in one portion and the mixture was stirred at 0 ºC for 20 min. The reaction mixture was diluted with diethyl ether, filtering through a Celite® pad. The filtrate was washed with sodium

thiosulfate solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a crude oil. Chromatography on silica gel afforded the corresponding *gem*-iodo boronate.

Spectral data of compound 93

2-(2-cyclopropyl-1-iodo-2-phenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



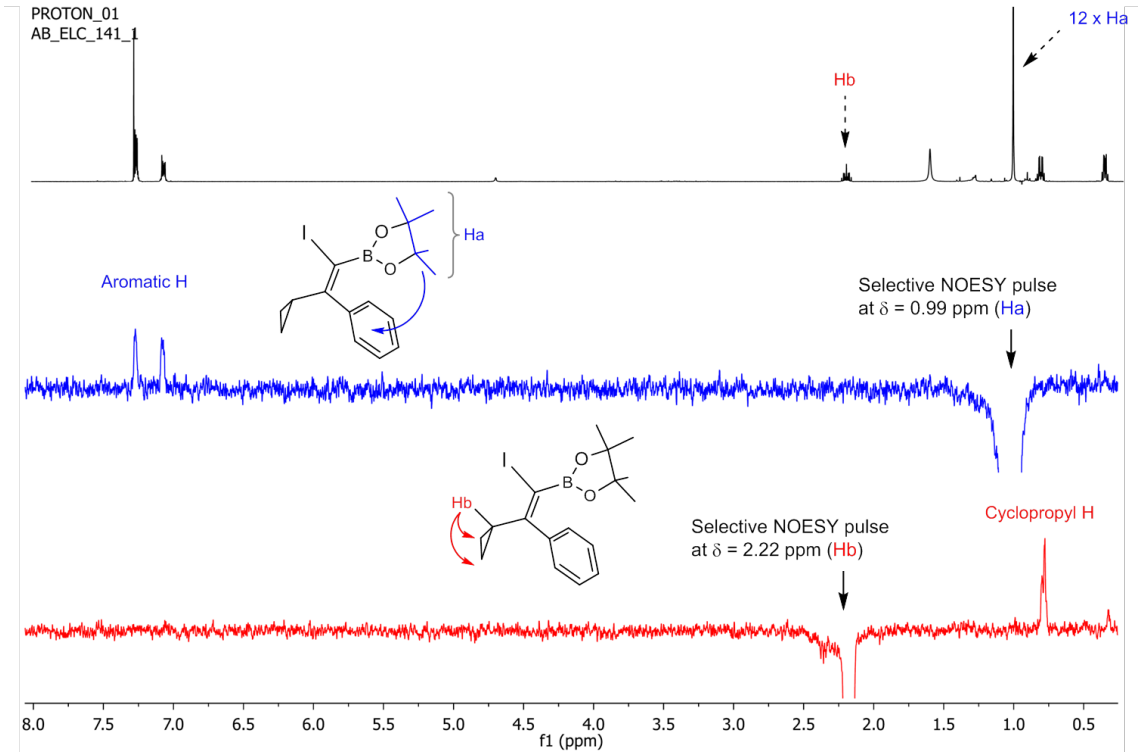
Flash column chromatography (hexane: ethyl acetate = 50:1) yielded 93 (87 %; ≥ 95 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.22 (m, 3H), 7.08–7.02 (m, 2H), 2.17 (tt, *J* = 8.3, 5.2 Hz, 1H), 0.98 (s, 12H), 0.81–0.75 (m, 2H), 0.36–0.29 (m, 2H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 159.6, 138.3, 129.3, 127.7, 127.6, 83.9, 24.2, 23.5, 6.3. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 28.6.

HRMS (EI) for $C_{17}H_{22}BIO_2$ $[M]^+$: calculated: 396.0758, found: 396.0751.

Polarization transfer NMR experiments to determine configuration of compound 93.

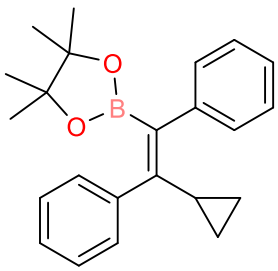
Based on the 1D selective NOE NMR experiments the configuration of isomer **93** was confirmed.



IV. c. Suzuki-Miyaura cross-coupling with gem-iodo boronates: General procedure F:

An oven dried resealable Schlenk tube equipped with a stirring bar was charged with $Pd(PPh_3)_4$ (4 mol%; 0.003 mmol) and toluene (0.1 M respect to the *gem*-iodo boronate). To this solution, the corresponding *gem*-iodo boronate (1 equiv.), boronic acid (1.5 equiv.), tetrabutylammonium bromide (TBAB) (10 mol %), and 2 M K_2CO_3 aqueous solution (3 equiv.) were added at room temperature under an Ar atmosphere. The reaction mixture was heated to 90 °C and stirred for 12 h. After completion (by TLC), the mixture was cooled to room temperature diluted with DCM. The mixture was filtered through a small pad of Celite® and anhydrous $MgSO_4$. Afterwards the solvent was concentrated at the rotary evaporator and the NMR yield calculated through internal standard (naphthalene). The resulting crude product was purified by column chromatography (silica gel) to give a coupled compound.

2-(2-cyclopropyl-1,2-diphenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

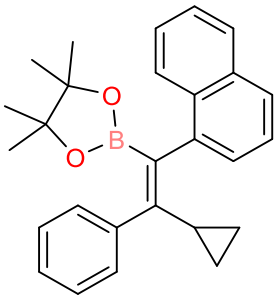


Flash column chromatography (hexane 100 % to hexane: ethyl acetate 75:1) yielded **94** (80 %; ≥ 95 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.41 (m, 2H), 7.41–7.33 (m, 2H), 7.33–7.19 (m, 6H), 1.91 (tt, J = 8.4, 5.3 Hz, 1H), 0.94 (s, 12H), 0.62–0.55 (m, 2H), 0.39–0.32 (m, 2H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 152.7, 141.0, 139.8, 130.1, 129.4, 128.1, 127.4, 126.9, 125.9, 83.2, 24.4, 15.0, 5.9. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 30.6.

HRMS (APCI) for $C_{23}H_{28}BO_2$ $[M+H]^+$: calculated: 347.2180, found: 347.2181.

2-(2-cyclopropyl-1-(naphthalen-1-yl)-2-phenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

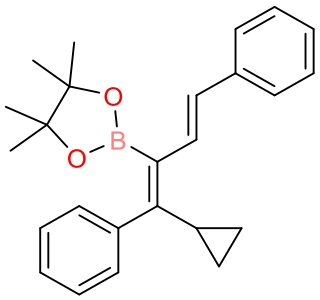


Flash column chromatography (hexane 100 % to hexane: ethyl acetate 25:1) yielded **95** (89 %; ≥ 95 % *E*)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.19 (m, 1H), 7.91–7.83 (m, 1H), 7.80–7.73 (m, 1H), 7.53–7.47 (m, 4H), 7.37–7.28 (m, 5H), 1.49–1.43 (m, 1H), 0.90 (s, 6H), 0.81 (s, 6H), 0.49–0.28 (m, 4H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 155.1, 139.7, 139.2, 133.8, 132.2, 130.1, 128.9, 128.2, 127.3, 126.9, 126.7, 126.5, 126.4, 125.8, 125.6, 125.5, 83.0, 24.3, 24.2, 15.6, 5.9, 5.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 31.0.

HRMS (EI) for $C_{27}H_{29}BO_2$ $[M]^+$: calculated: 396.2261, found: 396.2269.

2-((1E,3E)-1-cyclopropyl-1,4-diphenylbuta-1,3-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Flash column chromatography (hexane 100% to hexane: ethyl acetate 50:1) yielded **96** (49 %; ≥ 95 % *E*).

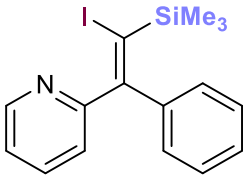
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.3 Hz, 1H), 7.43 (apparent d, *J* = 7.3 Hz, 2H), 7.36–7.12 (m, 8H), 6.66 (d, *J* = 16.3 Hz, 1H), 2.16 (tt, *J* = 8.4, 5.3 Hz, 1H), 1.03 (s, 12H), 0.82–0.74 (m, 2H), 0.39–0.32 (m, 2H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 152.8, 141.1, 138.5, 131.5, 129.7, 128.7, 128.6, 127.5, 127.1, 127.0, 126.4, 83.5, 24.7, 14.0, 6.2. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 32.1.

HRMS (APCI) for $C_{25}H_{30}BO_2$ $[M+H]^+$: calculated: 373.2335, found: 373.2338.

IV. d. Iododesilylation of compound 82 following General Procedure E:

Spectral data of 97:

2-(2-iodo-1-phenyl-2-(trimethylsilyl)vinyl)pyridine

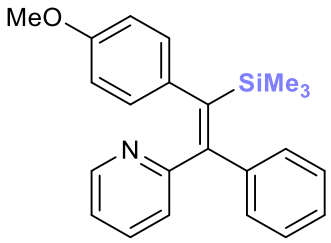


Flash column chromatography (hexane: ethyl acetate 35:1) yielded **97** (69 %; ≥ 99 % *Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (apparent d, *J* = 4.2 Hz, 1H), 7.67 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29 (apparent s, 5H), 7.27–7.21 (m, 1H), 7.17 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 0.02 (s, 9H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 164.6, 160.1, 149.4, 141.4, 136.7, 128.9, 128.3, 128.2, 123.0, 122.4, 113.6, 1.0. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ 3.2.

HRMS (EI) for $C_{15}H_{15}INSi$ $[M\text{-}CH_3]^+$: calculated: 364.0019, found: 364.0034.

2-(2-(4-methoxyphenyl)-1-phenyl-2-(trimethylsilyl)vinyl)pyridine

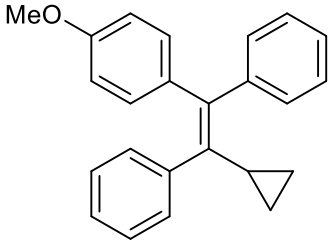


Flash column chromatography (hexane 100 % to hexane: ethyl acetate 27:1) yielded **98** (63 %; ≥ 99 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.45 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.37–7.26 (m, 4H), 6.92–6.82 (m, 4H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), -0.19 (s, 9H).**^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 161.3, 157.2, 153.4, 148.6, 142.7, 135.8, 135.6, 130.0, 129.6, 128.1, 127.5, 124.6, 120.9, 112.9, 55.2, 0.4. **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -5.3.

HRMS (EI) for $C_{22}H_{22}NOSi$ $[M\text{-}CH_3]^+$: calculated: 344.1471, found: 344.1469.

1-cyclopropyl-2-(4-methoxyphenyl)ethene-1,2-diyl)dibenzene

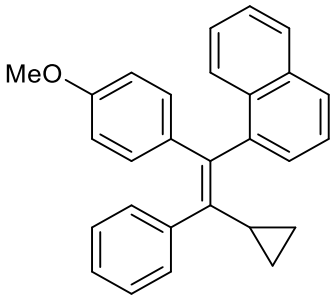


Flash column chromatography (hexane: ethyl acetate 75:1) yielded **99** (74 %; ≥ 99 % *Z*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.31 (m, 4H), 7.30–7.22 (m, 1H), 7.19–7.01 (m, 5H), 6.79–6.75 (m, 2H), 6.55–6.48 (m, 2H), 3.66 (s, 3H), 1.76 (tt, *J* = 8.4, 5.4 Hz, 1H), 0.64–0.57 (m, 2H), 0.38–0.31 (m, 2H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 157.1, 143.3, 140.3, 138.7, 138.6, 135.8, 131.5, 131.0, 130.5, 127.8, 127.3, 126.3, 126.0, 112.5, 54.9, 29.7, 16.3, 6.4.

HRMS (EI) for $C_{24}H_{22}O$ $[M]^+$: calculated: 326.1671, found: 326.1677.

1-(2-cyclopropyl-1-(4-methoxyphenyl)-2-phenylvinyl)naphthalene

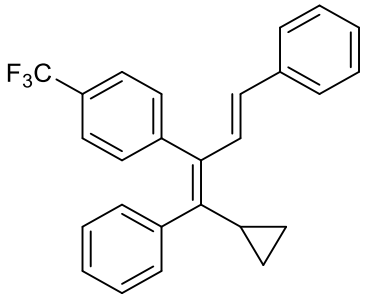


Flash column chromatography (hexane 100 %) yielded **100/100'** (22 %; 85:15 *E/Z*). NMR values are for the mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.18 (m, 0.85 x 1H **100**), 8.04 (dd, *J* = 8.2, 0.8 Hz, 0.15 x 1H **100'**), 7.91–7.86 (m, 0.85 x 1H **100**), 7.81 (dd, *J* = 7.1, 2.2 Hz, 0.85 x 1H **100**), 7.66–7.62 (m, 0.15 x 1H **100'**), 7.54–7.46 (m, 0.85 x 4H **100**), 7.39–7.29 (m, 0.15 x 4H **100'**), 7.28–7.22 (m, 0.85 x 2H **100**), 7.21–7.13 (m, 0.85 x 3H **100**), 6.94–6.86 (m, 0.15 x 5H **100'**), 6.85–6.79 (m, 2H), 6.49–6.42 (m, 2H), 3.77 (s, 0.15 x 3H **100'**, 3.61 (s, 0.85 x 3H **100**), 2.28–2.08 (m, 1H), 1.39–1.30 (m, 0.15 x 4H **100'**), 0.47–0.23 (m, 0.85 x 4H **100**). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 157.2, 142.0, 141.0, 138.5, 136.1, 135.2, 134.0, 132.3, 131.2, 131.0, 130.8, 130.0, 128.5, 128.3, 128.0, 127.9, 127.7, 127.1, 126.8, 126.6, 126.5, 126.1, 126.0, 125.8, 125.4, 125.2, 125.0, 113.3, 112.7, 55.3, 55.0, 16.7, 15.9, 6.7, 6.4, 5.6, 5.5.

HRMS (EI) for $C_{28}H_{24}O$ $[M]^+$: calculated: 376.1827, found: 376.1828.

((1Z,3E)-1-cyclopropyl-2-(4-(trifluoromethyl)phenyl)buta-1,3-diene-diyl)dibenzene



Flash column chromatography (hexane 100 %) yielded **101** (65 %; ≥ 95 % *Z*).

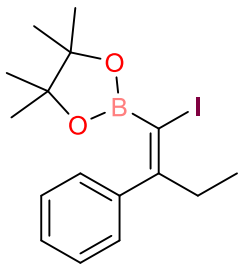
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.38 (m, 4H), 7.31 (m, 2H), 7.25–7.21 (m, 1H), 7.11 (apparent d, *J* = 7.9 Hz, 2H), 7.08–6.99 (m, 3H), 6.89–6.82 (m, 2H), 6.06 (d, *J* = 16.1 Hz, 1H), 2.30–2.18 (m, 1H), 0.97–0.88 (m, 2H), 0.48–0.40 (m, 2H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 144.6, 144.0, 139.2, 137.8, 137.4, 132.5, 131.4, 130.3, 128.8, 128.5 (q, *J* = 246 Hz), 128.1, 127.7, 127.4, 126.6, 126.4, 124.6 (q, *J* = 3.7 Hz), 14.4, 7.0. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.4.

HRMS (EI) for $C_{26}H_{21}F_3$ $[M]^+$: calculated: 390.1595, found: 390.1593.

V. Synthesis of Z-Tamoxifen via gem-silyl boronates:

Spectral data of gem-iodo boronate 102:

2-(1-iodo-2-phenylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



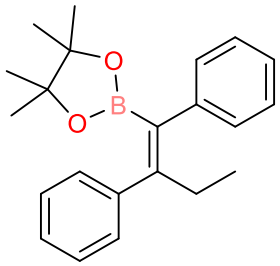
Prepared following *General Procedure E* from compound **76**. Flash column chromatography (hexane: ethyl acetate = 75:1) yielded **102** (88 %; ≥ 95 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 3H), 7.25–.21 (m, 2H), 2.73 (q, *J* = 7.5 Hz, 2H), 1.07 (s, 12H), 0.95 (t, *J* = 7.5 Hz, 3H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 160.3, 141.4, 128.2, 128.0, 127.9, 127.4, 84.2, 36.5, 24.3, 11.6. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 28.8.

HRMS (EI) for $C_{16}H_{22}BIO_2$ $[M]^+$: calculated: 384.0758, found: 384.0753.

Spectral data of vinyl boronate 103:

2-(1,2-diphenylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



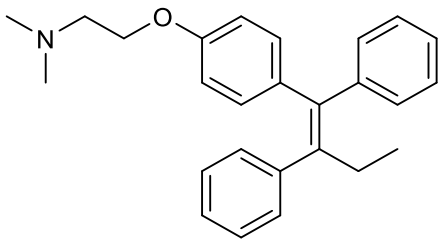
Prepared following *General Procedure F* from compound **102**. Flash column chromatography (hexane: ethyl acetate = 70:1) yielded **103** (98 %; ≥ 94 % *E*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.17 (m, 10H), 2.43 (q, *J* = 7.5 Hz, 2H), 1.00 (s, 12H), 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 153.9, 143.7, 141.6, 128.5, 128.5, 128.3, 128.0, 127.2, 126.0, 83.4, 27.3, 24.5, 13.4. **^{11}B NMR** (128.3 MHz, $CDCl_3$) δ 30.9.

HRMS (EI) for $C_{22}H_{27}BO_2$ $[M]^+$: calculated: 334.2104, found: 334.2091.

*Synthesis of Tamoxifen (≥ 93 % Z) from compound **103**.*

An oven dried resealable Schlenk tube equipped with a stirring bar was charged with Pd(*t*-$Bu_3P)_2$ (5 mol%) and dry THF (0.5 mL). To this solution the corresponding vinyl boronate **103** (1 equiv), dissolved in 0.5 mL of THF, 2-(4-iodophenoxy)-*N*,*N*-dimethylethan-1-amine (1.15 equiv) and a 3M NaOH solution (3 equiv) were added in sequence and the reaction was heated up at 60 °C for 24h. After completion (by TLC), the mixture was cooled to room temperature diluted with DCM. The mixture was filtered through a small pad of Celite® and anhydrous $MgSO_4$. Afterwards the solvent was concentrated at the rotary evaporator and the NMR yield calculated through internal standard (naphthalene). The resulting crude product was purified by column chromatography (silica gel) to afford compound **104**.



Flash column chromatography (hexane: dichloromethane [treated with 30 % ammonium hydroxide] = 1:1 yielded **104** (65 %; (≥ 93 % Z). *Only major diasteromer data are given.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2H), 7.31–7.23 (m, 3H), 7.21–7.09 (m, 5H), 6.78 (apparent d, *J* = 8.8 Hz, 2H), 6.57 (apparent d, *J* = 8.8 Hz, 2H), 3.97 (t, *J* = 5.7 Hz, 2H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.47 (q, *J* = 7.4 Hz, 2H), 2.34 (s, 6H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C {^{1}H} NMR** (100.6 MHz, $CDCl_3$) δ 156.7, 143.9, 142.5, 141.4, 138.3, 135.7, 132.0, 129.8, 129.6, 128.2, 128.0, 126.6, 126.1, 113.5, 65.5, 58.3, 45.9, 29.1, 13.7.

HRMS (EI) for $C_{26}H_{29}NO$ $[M]^+$: calculated: 371.2249, found: 371.2261.

4.6 References

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UNIVERSITAT ROVIRA I VIRGILI
SELECTIVE POLYFUNCTIONAL SYNTHESIS THROUGH ORGANOBORON COMPOUNDS
Enrico La Cascia

Chapter 5.

Conclusions.

Chapter 2

In this chapter, we have developed the first example of metal-free β-boration of in situ formed α,β-unsaturated imines, highlighting the compatibility of the organocatalytic Bpin addition with the imine formation in the presence of both ketone and amine. The reaction shows little dependence on the electronic properties of substrate and shows consistently high conversion. Importantly, the use of chiral phosphines, such as the diphosphine (*S*)-MeBoPhoz, enables the catalytic asymmetric version to be realized with moderate asymmetric induction. Interestingly, the enantioselectivity is higher than that induced by the same chiral phosphines when modified using the corresponding Cu(I)-based catalytic system. The mechanism of the organocatalytic β-boration of these α,β-unsaturated imines has been postulated from a theoretical point of view, and seems to necessarily involve quaternization of the diboron reagent with methoxide while the role of the phosphine has been regarded to the ion pair formation.

Chapter 3.

In this chapter we tried to exploit the boron chemistry, and, in particular, the β-borylation reaction towards the synthesis of bioactive compounds such as Tramadol. Inspired by the total synthesis of Duloxetine and Fluoxetine reported by our group we tried to develop a similar methodology consisting in the *in situ* formation of an imine intermediate, one-pot β-boration, transamination, reduction and oxidation. Unfortunately, after several attempts we could not achieve our goal.

We tried both catalytic and organocatalytic protocols to achieve the most challenging step: the β-borylation of the imine intermediate.
We could conclude that compounds that have a single bond with remarkable freedom of rotation adjacent to a C=N double bond are much less reactive towards the β-boration than those that are not affected from this conformational issue.

Chapter 4.

In this part we reported a new metal-free approach consisting in the insertion of a diazocompound, such as (trimethylsilyl)diazomethane, into the σ B-B bond to generate the useful adduct $HC(Bpin)_2(SiMe_3)$. This compound showed to be a efficient reagent for the synthesis of *gem*-silylboronates. These class of molecules demonstrated to be particularly versatile since they contain two different functional group.
In this context we were able to synthesize a wide range of gem-silylboronates with high regioselectivity.
Regarding further functionalization, the C-B bond could be easily transformed into C-C bond through Suzuki-Miyaura croos-coupling.
The most challenging transformation was the derivatization of the C-Si bond. As the Hiyama coupling resulted particularly hard, we applied a protocol called iododesylilation in order to switch the reactivity. We were pleased to see that we could generate a new species with high synthetic potential that gave access to tetrasubstituted olefines.
In this scenario we wanted also to demonstrated that our protocol was useful towards the synthesis of (*Z)*-Tamoxifen.

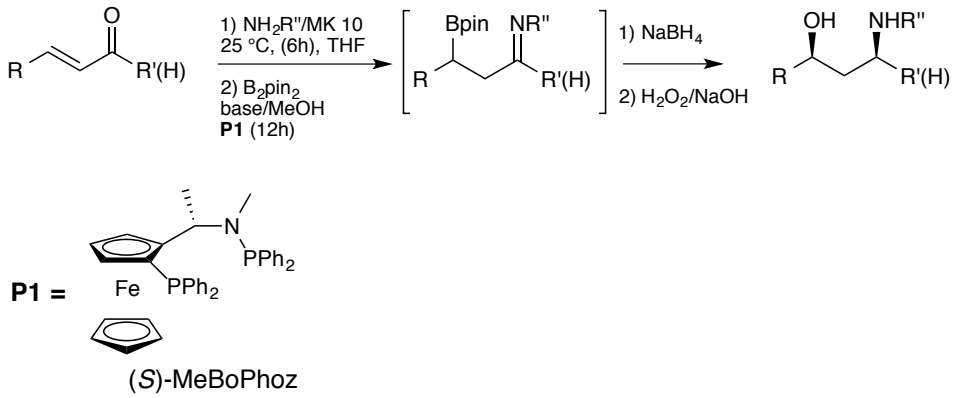
Chapter 6.

Summary.

The thesis has been focused on the application of boron chemistry and, in particular, on developing new methodologies. The first part covered the topic of the β-boration reaction towards the synthesis of γ-amino alcohols. A new metal-free approach to the β-borylation of α,β-unsaturated imines generated *in situ* has been reported. In this case the diboron compound, bis(pinacolato)diboron, is activated by a base/MeOH system which generates a nucleophilic boron moiety that can interact with a α,β-unsaturated acceptor (imine). This latter is activated by a catalytic amount of phosphine.

When a chiral phosphine such as (*S*)-MeBoPhoz is used, the β-borylation can be performed in an enantioselective manner with *ee* values up to 70%.

After a high diasteroselective protocol of reduction and oxidation we could provide the desired γ-amino alcohol. (Scheme 6.1).



Scheme 6.1. Asymmetric metal-free synthesis of γ-amino alcohols.

Interestingly, when a copper salt is modified with the (*S*)-MeBoPhoz ligand, the enantioselectivities dropped showing generally lower values of *ee* than the organocatalytic approach.

It has been tried to apply this chemistry to the synthesis of a bioactive compound such as Tramadol (Fig 6.1).

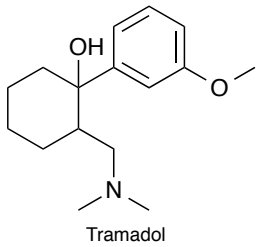
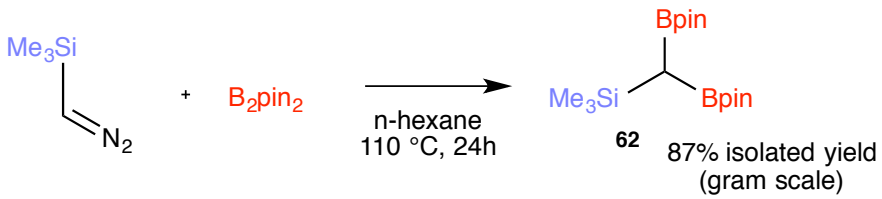


Fig 6.1. Structure of Tramadol

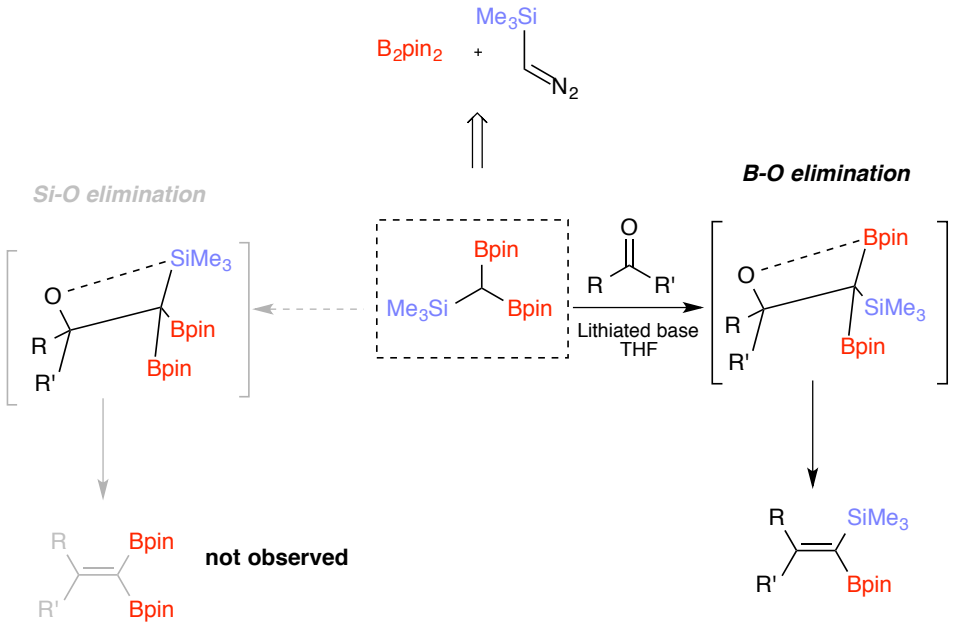
This part of the manuscript covered the attempts that were made to achieve the total synthesis. Many catalytic systems have been tried but unfortunately, none of them had positive results.

The last part of the thesis is based on the insertion of a diazocompound, such as (trimethylsilyl)diazomethane), to generate the *gem*-diboron compound **62.** (Scheme 6.2).



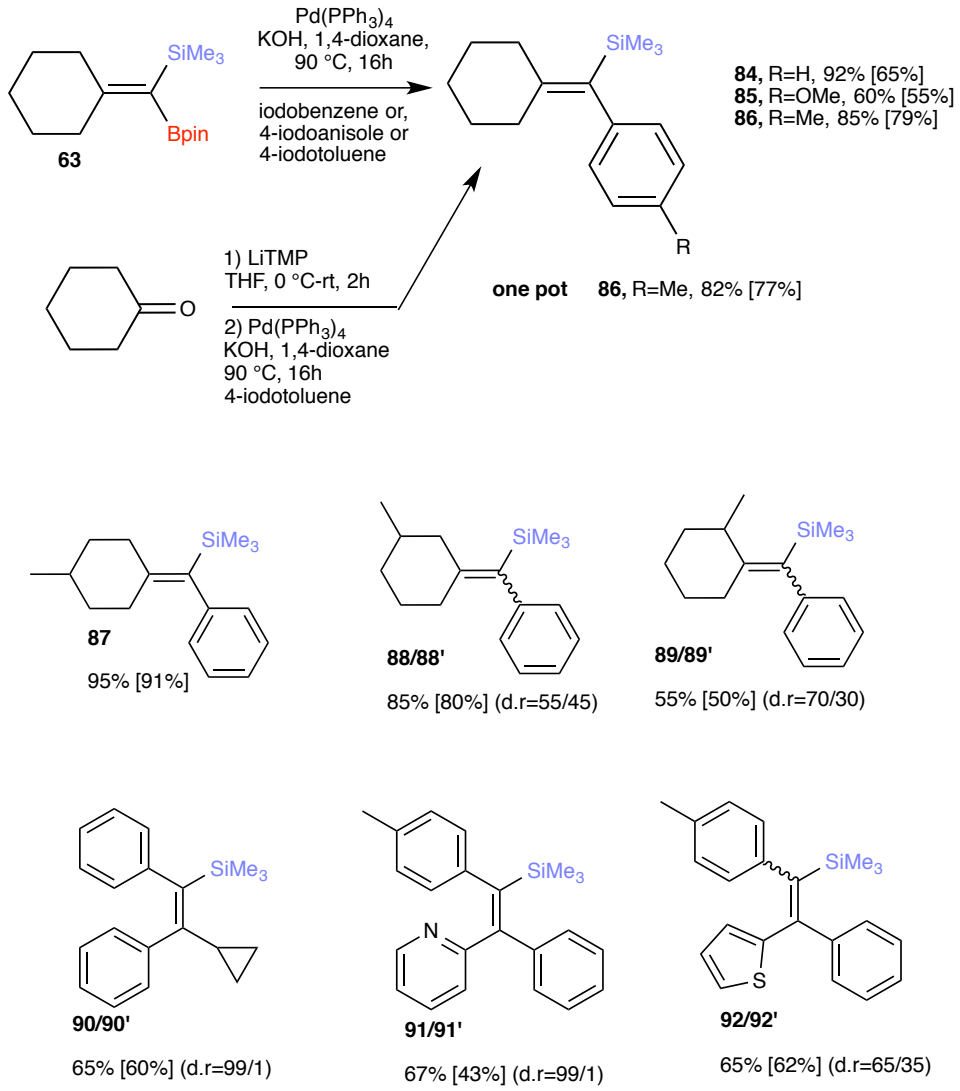
Scheme 6.2. Insertion of (trimethylsilyl)diazomethane into the σ B-B of B_2pin_2.

The treatment of compound **62** with a lithiated base, such as LiTMP, generated a stabilized carbanion which can attack carbonyl compounds like ketones to afford, after a Peterson-type B-O elimination, a *gem*-silylboron olefin (Scheme 6.3).



Scheme 6.3. Synthesis of *gem*-silylboronates.

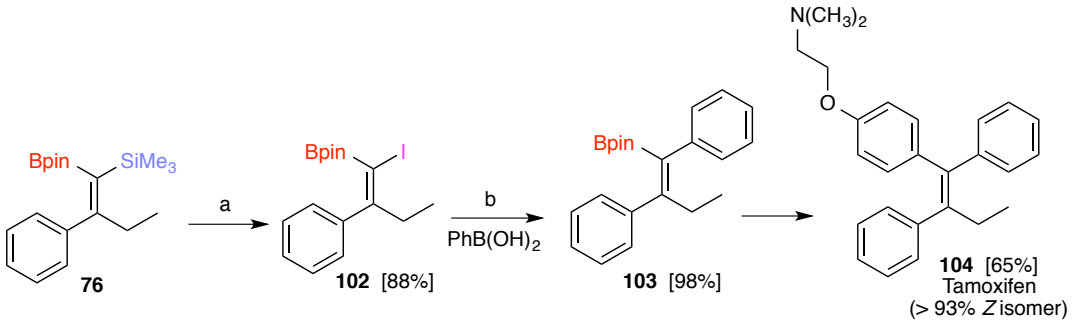
We demonstrated that further functionalizations, suck as Suzuki-Miyaura cross-coupling, could be performed (Scheme 6.4).



Scheme 6.4. Suzuki-Miyaura cross-coupling of *gem*-silylboronates

Even the more challenging iododesilylation was successfully achieved, allowing the synthesis of tetrasubstituted olefins after two consecutive cross-couplings.

Towards this aim, the synthesis of (*Z*)-Tamoxifen was conducted with high values of selectivity (ratio *Z*/*E* > 93:7) (Scheme 6.5).



Scheme 6.5. Formal synthesis of (*Z*)-Tamoxifen.