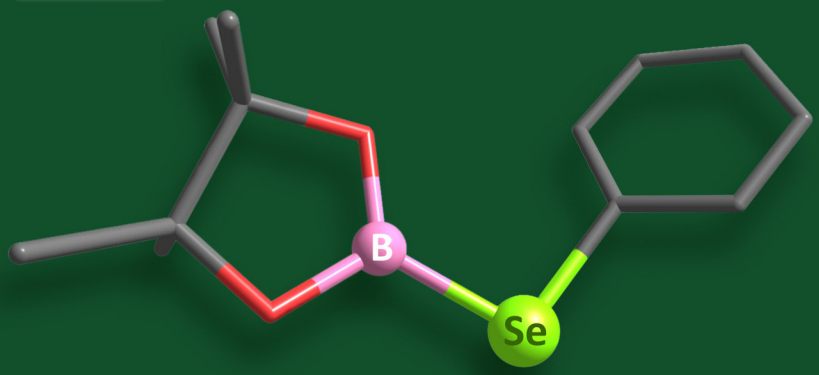
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES

Xavier Sanz López



DOCTORAL THESIS

Theoretical and experimental understanding of the pull-push effect of B on the synthesis of organo-boranes, -sulfides and -selenides

Xavier Sanz López

Universitat Rovira i Virgili

ICIQ Institut Català d'Investigació Química

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"Theoretical and experimental understanding of the pull-push effect of B on the synthesis of organo-boranes, -sulfides and -selenides"

DOCTORAL THESIS

Supervised by

Dr. Mª Elena Fernández Gutiérrez and **Dr. Carles Bo Jané**

Tarragona

2015

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Dra. Maria Elena Fernández, professora titular del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i Dr. Carles Bo de l'Institut Català d'Investigació Química,

FEM CONSTAR que aquest treball, titulat "*Theoretical and experimental understanding of the pull-push effect of B on the synthesis of organo-boranes, -sulfides and -selenides*", que presenta el Sr. Xavier Sanz López per a l'obtenció del títol de Doctor en Química, ha estat realitzat sota la nostra direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i a l'Institut Català d'Investigació Química i que acompleix els requeriments per a poder optar a la Menció Internacional.

Tarragona, 1 de setembre de 2015

Els directors de la tesi doctoral

Dra. Maria Elena Fernández

Dr. Carles Bo

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"Live as if you were to die tomorrow.
Learn as if you were to live forever."

Mahatma Gandhi

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"Nothing has such power to broaden the mind
as the ability to investigate systematically and truly
all that comes under thy observation in life."

Marcus Aurelius

1. Introduction and objectives

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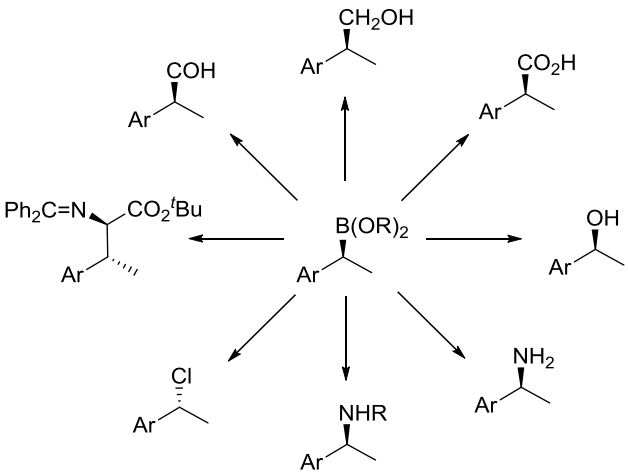
1.1 General overview on organoboranes

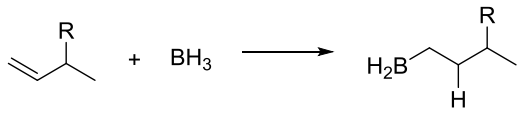
Nowadays, organoboranes are relevant compounds as they can be used as intermediates in the synthesis of many functionalized molecules.[1] Moreover, organoboron reagents have potential applications in biochemistry and biomedical sciences due to their biological activity.[2] Organoboranes can be easily prepared through well established protocols.[3] Particularly, the catalytic C-B bond formation is interesting because it serves as a platform for further transformations with total control of the chemo-, regio- and stereoselectivity of the product formation (Scheme 1.1).[4]



Scheme 1.1. Some of the typical transformations of the C-B bond.

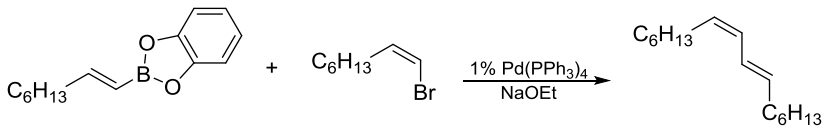
Boron reagents have been widely studied and utilized during the last century, disclosing a broad range of reactions and applications in many areas, especially in organic synthesis. A clear example was the 1979 Nobel Prize in Chemistry, awarded to H. C. Brown and Georg Wittig "*for their development of the use of boron and phosphorus-containing compounds, respectively, into important reagents in organic chemistry*".[5] In particular, H. C. Brown was pioneer in the hydroboration reaction.[6]

The hydroboration is described as the reaction of a borane reagent with unsaturated molecules and it is used to introduce a boryl moiety into the substrate. The addition occurs in a *syn*-manner and the boron moiety occupies the less hindered position (Scheme 1.2).



Scheme 1.2. General alkene hydroboration reaction.

This methodology revolutioned the synthetic chemistry since it allowed the regioselective addition of boron moieties which could be afterwards transformed into C-C,[7] C-N,[8] C-O and C-X bonds as well as homologated (Scheme 1.1).[9] Many other useful transformations have been discovered and reported in the literature[10] and subsequently, organoborons have become key reagents in organic synthesis.[3a, 11] Recently, Akira Suzuki was awarded as well, along with Richard F. Heck and Ei-ichi Negishi with the 2010 Nobel Prize in Chemistry "*for palladium-catalyzed cross-couplings in organic synthesis*" (Suzuki-Miyaura cross-coupling), using organoboron compounds (Scheme 1.3).[12]



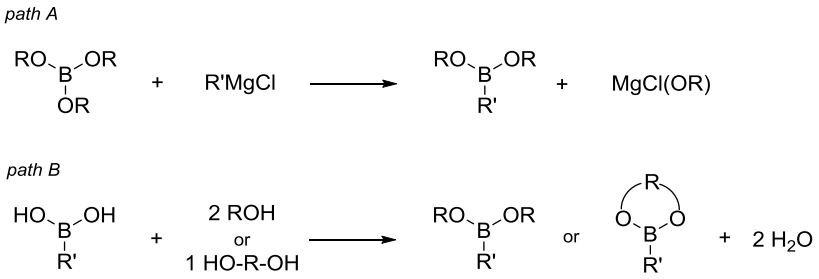
Scheme 1.3. Reaction scheme of a Suzuki-Miyaura cross-coupling.

Organoboronic esters are the most frequently used organoboranes in organic synthesis due to three main reasons:

a) They present relative stability to the air, water and silica gel chromatography depending on their structure. Thus, bulky, aliphatic and cyclic organoboronic ester compounds are, in general, easier to purify, store and handle while the unhindered, aromatic and acyclic ones are more unstable.[13] This fact is related to the partial donation of the lone pair of electrons of the oxygen atoms into the empty *p*-orbital of the boron.

b) Secondly, there is a large scope of organoboronic esters readily commercially available or easy to synthesize. There are two general synthetic routes to prepare organoboronic esters. The first one is the transmetallation of the corresponding trialkoxyborane with organomagnesium or organolithium reagents (Scheme 1.4, *path A*). This methodology is non convenient due to the low atom economy and the rigorously anhydrous conditions required.[3a, 14] The

second one (Scheme 1.4, *path B*) is the esterification of organoboronic acid with the corresponding alcohol or diol.[15]



Scheme 1.4. General synthetic methods of organoboronic esters.

These synthetic routes allow the modification of the backbone of the boryl moiety giving rise to a wide number of organoboronic esters. The nature of the substituent in the borane reagents changes their Lewis acidity and consequently their stability and reactivity (Figure 1.1).

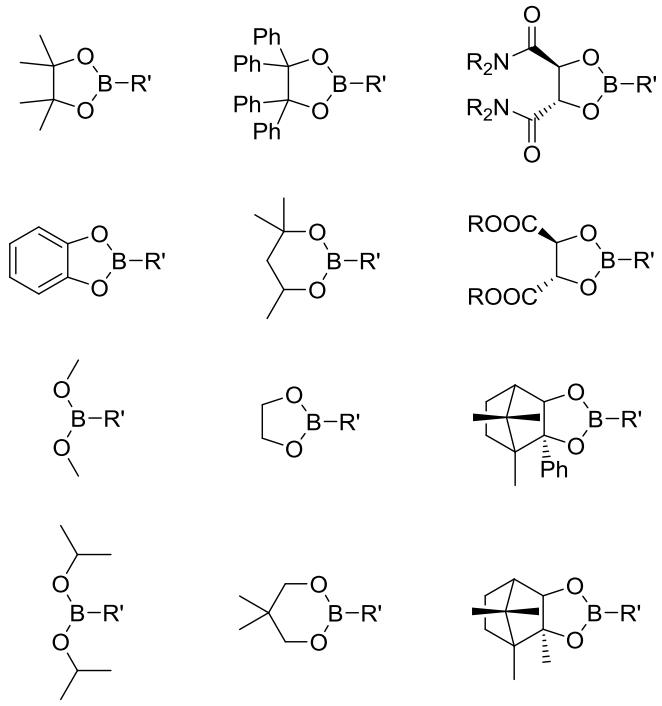
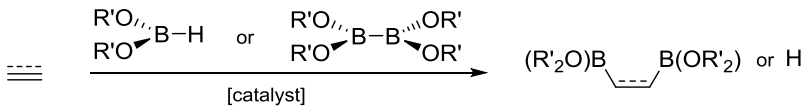


Figure 1.1. Palette of organoboronic esters.

c) The addition of organoboronic esters to unsaturated carbon-carbon bonds provides an alternative synthetic methodology to obtain organoboron compounds (Scheme 1.5).



Scheme 1.5. Alternative route to the synthesis of organoboron compounds by addition of the boron reagent to an unsaturated substrate.

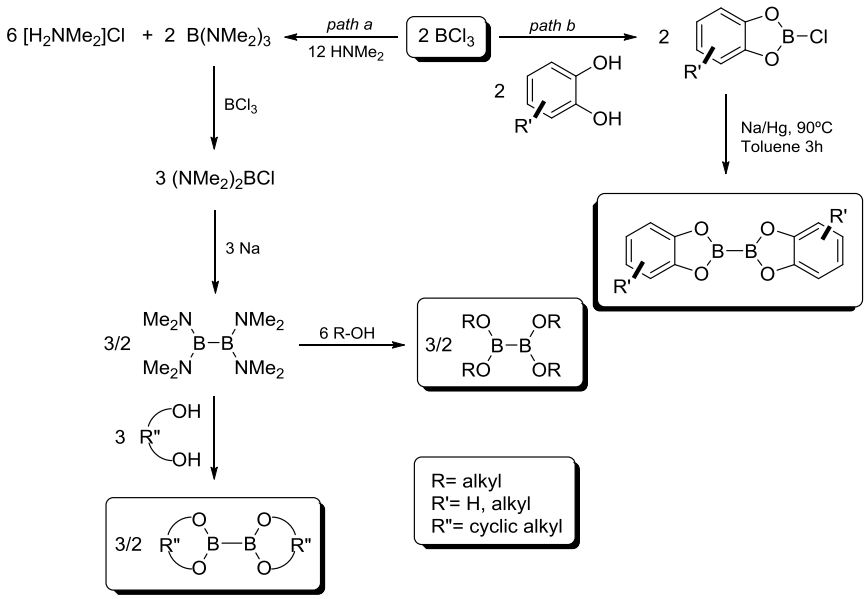
Taking into consideration the last point, the addition of a borane reagent to C=C or C≡C can be divided into two main groups depending on the nature of the borane reagent: hydroboranes ($HB(OR)_2$) and diboranes ($B_2(OR)_4$). In this thesis we focus on diboranes and their reactivity.

1.2 The diboron reagents. Synthesis and reactivity

Concerning the diboron reagents, tetraalkoxydiborons of general formula $B_2(OR)_4$ are more stable to the air, water and silica gel than B_2H_4,[16] B_2X_4[17] or B_2R_4.[18] But in some cases, depending on their structure they are less robust and quite sensible to the media.

Diboron tetrahalides (B_2X_4, X= Cl^-, F^-, Br^-) can react with alkenes and alkynes in the absence of any catalyst. However, these reagents are rather difficult to prepare and handle and are unstable towards disproportionation.[19] On the other hand, tetraalkoxydiborons are relatively easy to synthesize and are quite stable and easy to handle.

The synthesis of diboranes involves a multiple-step strategy based on the works of Brotheron and co-workers.[20] One of the best established methods involves the formation of tris(alkylamino)borane as an intermediate (Scheme 1.6, *path a*). This synthesis was developed by Nöth[21] and improved by Marder[22] and Srebnik.[23] Hartwig and co-workers reported an alternative synthesis from homocoupling of the halocatecholboranes[24] (Scheme 1.6, *path b*), failing in the synthesis of tetraalkoxydiboron reagents.



Scheme 1.6. Synthetic routes for the preparation of tetraalkoxydiborons.

A wide scope of diboron reagents can be synthesized through well established methods (Figure 1.2). Bis(pinacolato)diboron (B_2pin_2) and bis(catecholato)-diboron (B_2cat_2) are the most commonly used diborons due to its commercial availability. This type of $B_2(OR)_4$ compounds contain a 6-atom-5-σ-bond-8-π-electron system which results in a π-bond order of 0 between the two boron atoms. Thus, the net B-B bond order of 1 arises from the σ-bond alone. The B-B bond distance depends on the alkyl or aryl nature of the substituents. Therefore, for bis(catecholato)diboron the B-B distance (1.678 Å) is somewhat shorter than for bis(pinacolato)diboron (1.711 Å) or bis(neopentyl-glycolato)diboron (2.029 Å), within a comparative dihedral angle of 0º for the three structures.[22b]

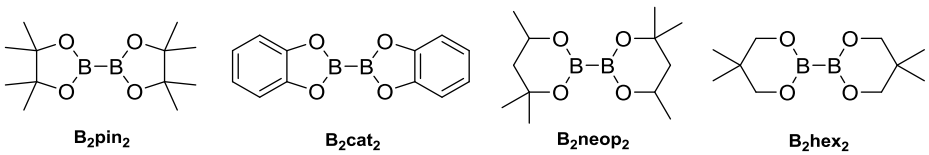
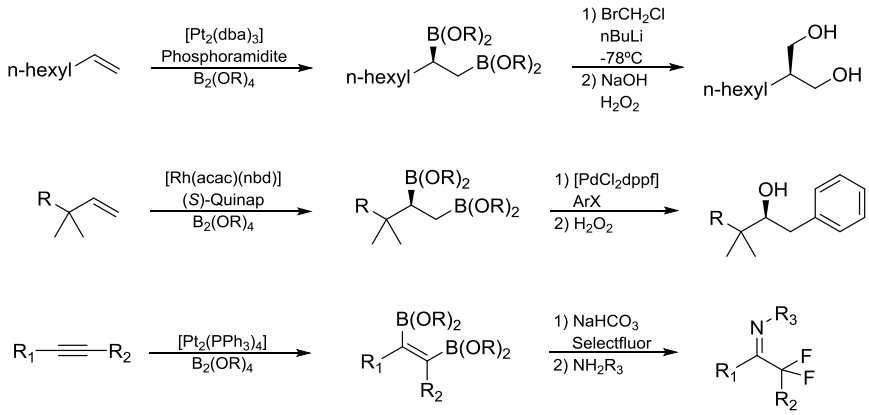


Figure 1.2. Diboron species B_2pin_2, B_2cat_2, B_2neop_2, B_2hex_2.

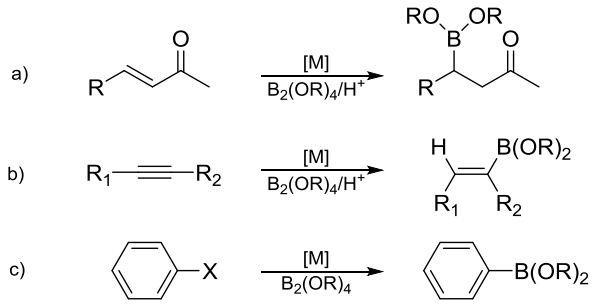
Diboron compounds are generally used to introduce simultaneously two boryl units into a substrate molecule. Their addition to unsaturated carbon-carbon bond proceeds in *syn* fashion. The diboration reaction is an atom economical

and very versatile procedure because both boryl units can be transformed independently into different functional groups (Scheme 1.7).[25]



Scheme 1.7. Examples of catalytic diboration reactions and subsequent independent transformations of the C-B bonds.

However, diboron reagents present different behavior depending on the reaction conditions and the nature of the substrate they react with. Thus, other less atomic economical reactions such us *β*-boration, hydroboration and borylation of unsaturated compounds can happen (Scheme 1.8).



Scheme 1.8. Alternative reactions of diboranes: *β*-boration (a), hydroboration (b) and borylation (c).

It is well known that the B-B bond is rather strong (104 kcal·mol^{-1})[22a] and this might be the cause of the unsuccessful direct addition of diboron reagents to C-C multiple bonds.[26] Therefore, tetralkoxydiborons need to be activated to react with unsaturated substrates. The most extended method to activate diboron reagents is mainly performed by transition metal catalysts *via* homolytic oxidative addition or *via* σ-bond metathesis although nowadays the organocatalytic approaches are getting more relevance.

1.2.1 Activation of diboron reagents by transition metal catalysts

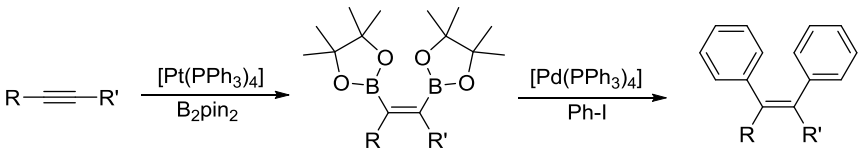
1.2.1.1 Activation *via* oxidative addition

Diborons can be oxidatively added to low valent late transition metals through the B-B bond cleavage, subsequently allowing the catalytic transfer of the diboron reagent to unsaturated organic substrates,[27] due to the kinetic lability of the resulting boryl-metal complexes. Thus, the use of transition metal complexes guarantees, first, the activation of tetraalkoxy- and tetraaryloxydiborons by oxidative addition, and second, the reductive elimination towards the diboron products in a catalytic cycle.[28]

The use of an adequate transition metal complex facilitates the control of the chemo- and regioselectivity in the formation of the new C-B bonds. In addition, the modification of the catalyst precursor with chiral ligands opens the door to the enantioselective formation of these bonds.

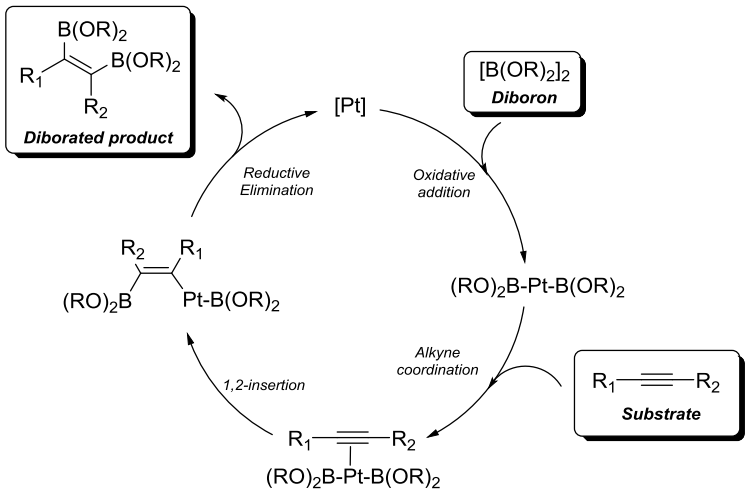
The boryl-metal complexes are the key species of a catalytic cycle in which several consecutive steps transform unsaturated molecules into mono- and diborated compounds.[29]

Bearing in mind that metal-promoted 1,2-diboration offers many advantages over the uncatalyzed reaction, researchers have been exploring and improving catalytic systems since Miyaura and co-workers' first report.[30] They were pioneers in the catalyzed diboration of alkynes using platinum-phosphine systems as catalytic precursors. They reported that tetrakis (triphenylphosphine)platinum(0), [$Pt(PPh_3)_4$], catalyzed the clean addition of B_2pin_2 to both terminal and internal alkynes, resulting in the formation of *cis*-alkene bis-boronate esters. The two C-B bonds formed in this reaction were transformed into two C-C bonds through the previously mentioned palladium-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 1.9).[30]



Scheme 1.9. First Pt-catalyzed diboration of alkynes reported by Miyaura and Suzuki and next derivatization through cross coupling reaction.

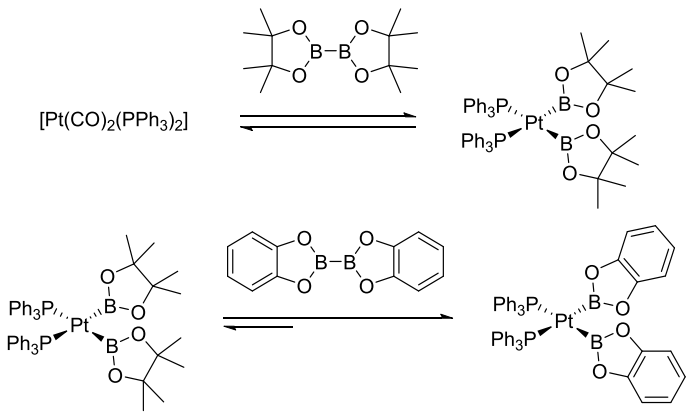
Miyaura and co-workers also reported spectroscopic evidences for the formation of the *cis*-bis(boryl)metal complex *cis*-[$Pt(PPh_3)_2(Bpin)_2$], which was isolated and structurally characterized by single-crystal X-ray diffraction confirming that the diboron reagent was added to the metal center *via* oxidative addition. Taking into account this information the authors proposed the following catalytic cycle (Scheme 1.10). The oxidative addition of diboron reagents to the metal center is followed by coordination of the substrate, 1,2-insertion into the M-B bond, finishing with the reductive elimination that regenerates the active species and provides the diborated product. Subsequent experimental [31] and theoretical studies were in accordance with this proposal.[32]



Scheme 1.10. Pt-mediated mechanism for the diboration reaction proposed by Suzuki and co-workers.

Importantly, the nature of the diboron reagent was found to be critical in the relative stability of the resulting bisboryl-Pt(II) species. [$Pt(Bpin)_2(PPh_3)_2$] with B_2cat_2 gave [$Pt(Bcat)_2(PPh_3)_2$] and B_2pin_2, suggesting stronger Pt-B bonding interactions in Pt-Bcat rather than in Pt-Bpin, (Scheme 1.11).[33] The presence of sp^2 carbons, and the aromatic ring capability of removal electron density from the oxygen atoms, causes the B-O bonds in Bcat to be weaker than those in Bpin. The pair of electrons in the σ bond with the metal center is less electron releasing for M-Bcat than M-Bpin, therefore Bcat exert a weaker *trans* influence than Bpin.[29, 34] Thus, formation of [$Pt(Bcat)_2(PPh_3)_2$] and B_2pin_2 is thermodynamically favored over [$Pt(Bpin)_2(PPh_3)_2$] and B_2cat_2. The reaction

takes place in the *inner* coordination sphere of the transition metal and gives the *syn* diborated products.



Scheme 1.11. Addition of B_2pin_2 to Pt(0) complex and the relative stability of the metal-boryl species.

Along with Pt complexes, Rh(I) complexes were also explored in the activation of the diboron reagents towards the diboration reaction.

The nature of the catalytic system in diboration reaction is crucial. Both transition metal complexes modified with phosphorous ligands and also phosphine-free metal complexes have been tested,[31] but in all these approaches the catalytic diboration of alkenes gave a complex mixture of hydroborated, diborated and triborated organoboron products.[35]

This complex reaction outcome can be understood from a mechanistic point of view. The catalytic cycle starts with an oxidative addition of the diboron reagent to the metal center, leading to a metal-diboryl complex, as explained previously in the Scheme 1.10 for the Pt system. The desired 1,2-diborated product arises from the alkene insertion into a M-B bond and a subsequent reductive elimination. However, a *β*-hydride elimination reaction competes with the reductive elimination yielding the monoborated alkene species and a $[RhH(B(OR)_2)L_2]$ species capable to produce hydroborated product.

The nature of the boryl moiety also influences the ratio of the products.[35] For instance the diborons B_2pin_2 or B_2neop_2 seem to favor the *β*-hydride elimination versus the reductive elimination and on the other hand B_2cat_2 seems to favor the reductive elimination and consequently the 1,2-diboration, when the

catalyst precursor is *trans*-[RhCl(CO)(PPh_3)$_2$] in the presence of CH_3CN as solvent.[36] Alternatively, the activation of B_2cat_3 (Figure 1.3) by [Rh(acac)L_2] provides a zwitterionic complex, which facilitates the reductive elimination towards the 1,2-diborated product, disfavoring the *β*-H elimination step.[37]

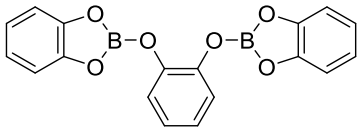
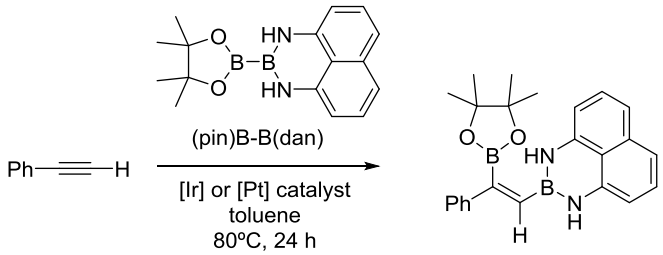


Figure 1.3. Tris(catecholato)diboron (B_2cat_3).

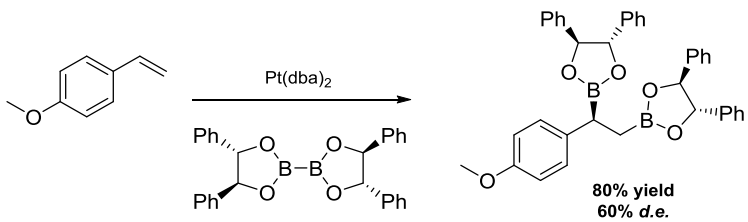
Alternative strategies with different catalytic systems have lead to high chemoselectivities in the formation of organodiboronic esters from C=C, C=N and C=S substrates.[38]

In 2010, it was demonstrated that an unsymmetrical diboron reagent can regioselectively be added to terminal alkynes in the presence of Ir or Pt catalyst, leading to the formation of 1-alkene-1,2-diboron derivatives, in which the internal boryl moiety (Bpin) is more reactive towards further functionalization (Scheme 1.12).[39]



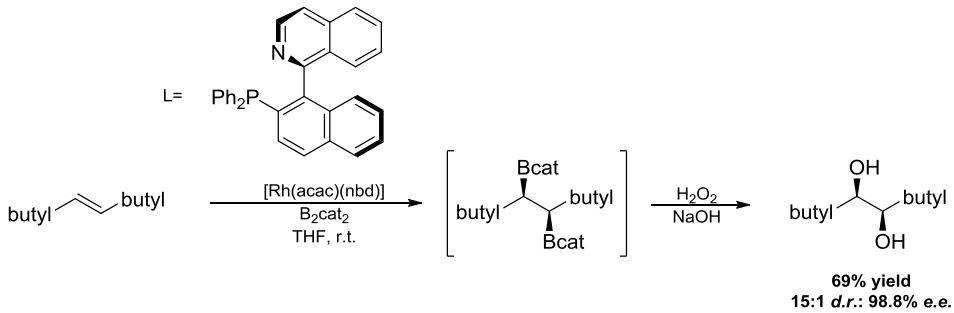
Scheme 1.12. Example of diboration of alkynes with unsymmetrical diboron agent.

The first asymmetric catalytic diboration attempts were carried out by Marder and co-workers using chiral diboron reagents.[40] They studied the platinum mediated addition of enantiomerically pure chiral diboron compounds to vinylarenes. The reaction resulted to be very slow and after 3 days of reaction time at 4ºC, 80% of diborated product was obtained with a diastereomeric excess (*d.e.*) of 60% (Scheme 1.13).



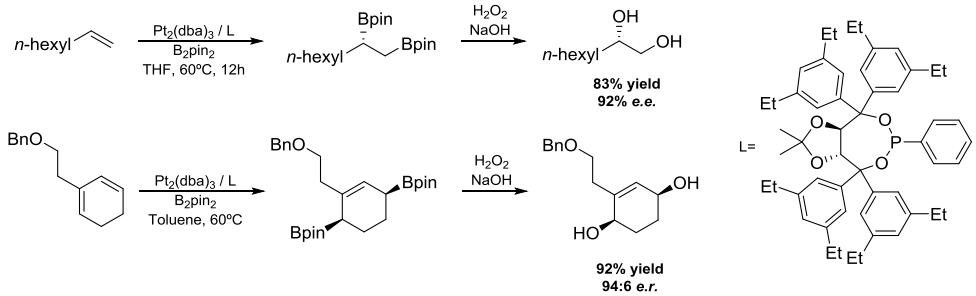
Scheme 1.13. First reported reaction of asymmetric diboration.

Later on, the modification of transition metal complexes with chiral ligands opened new doors for asymmetric induction. Morken and co-workers were pioneers in the field of enantioselective diboration reaction of alkenes, by modification of rhodium complexes with the P,N-ligand (*R*)-QUINAP (Scheme 1.14).[41]



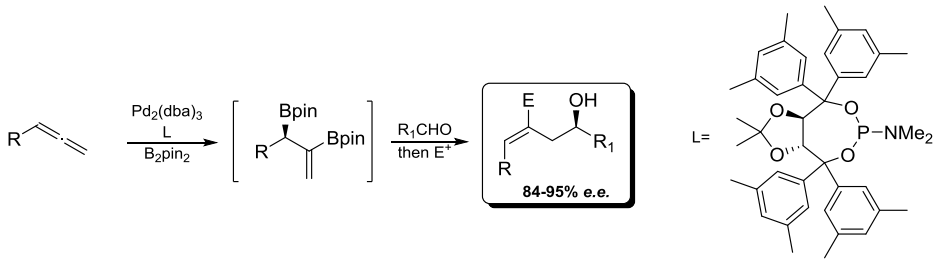
Scheme 1.14. An example of enantioselective diboration of simple alkenes with (*R*)-QUINAP.

Morken and co-workers next described a very active and selective Pt catalytic system modified with chiral phosphonites (with TADDOL backbone) achieving enantioselectives up to 92% for a large scope of terminal alkenes.[25c] They also developed catalytic systems towards the enantioselective diboration of cyclic dienes.[42] In contrast to the previous studies, this platinum/phosphonite system is the first catalytic system providing high enantioselectivity using B_2pin_2 as the diboron source (Scheme 1.15).



Scheme 1.15. Examples of enantioselective diboration of simple alkenes and cyclic dienes with Pt/Phosphonite system.

Mono- and dinuclear palladium species have been proved to work by Morken and co-workers in the asymmetric diboration of allenes giving moderate to high selectivities (Scheme 1.16).[43] Theoretical studies have also been performed in the Pd(0) catalyzed diboration.[44]

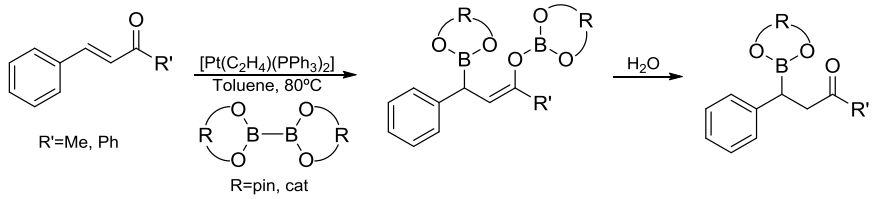


Scheme 1.16. Pd/phosphoramidite catalyzed enantioselective diboration and subsequent derivatization of allenes.

Tetranuclear palladium species have also been shown to mediate the diboration of vinylarenes and aliphatic 1-alkenes, under mild and basic reaction conditions, producing a variety of 1,2-diborated compounds in excellent yields and chemoselectivities.[45] On the other hand, B_2cat_2 promotes the reduction of Pd(II) into Pd(0) nanoparticles which seem to be responsible for the catalytic diboration[45] as it was also demonstrated for an analogue example from Au(I) to Au(0)-nanoparticles.[46]

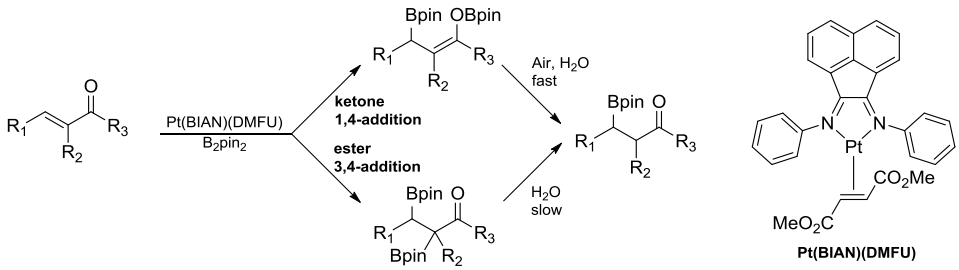
Among activated olefins, *α,β*-unsaturated carbonyl compounds are challenging substrates because the carbonyl functional group has a direct electronic influence on the double bond. It is reported that the use of hydroboranes directly reduces the carbonyl group; however the use of diboron compounds allows the 1,4-diboration reaction.

The first 1,4-diboration of *a,β*-unsatured carbonyl compounds was carried out by Marder and co-workers[47] with platinum complexes. They described the reaction as a 1,4-diboration, which generated the corresponding *β*-borated product after the hydrolytic work up (Scheme 1.17). The *β*-boration reaction has a poor atom economy because only one boryl unit from the diboron reagent is incorporated into the final product.



Scheme 1.17. First catalytic *β*-boration of *a,β*-unsatured ketones.

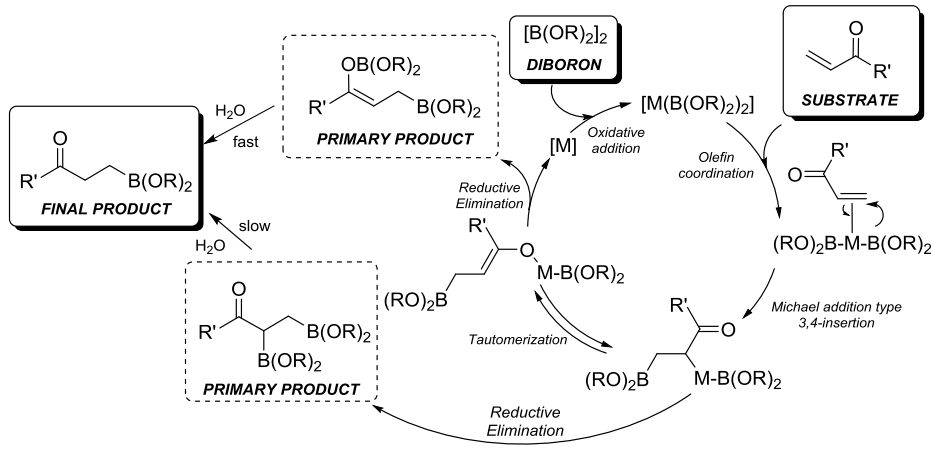
Marder and co-workers[48] focused their efforts on the observation and isolation of diborated intermediates, consequently contributing to the understanding of the mechanisms of the metal catalyzed *β*-boration reaction. They observed that the second generation of Pt(0) catalyst (Scheme 1.18) displayed different reactivity between *a,β*-unsaturated ketones and esters. The activated ketones gave the expected 1,4-diboration and the activated esters formed the unprecedented 3,4-diborated products.



Scheme 1.18. *β*-boration of *a,β*-unsaturated ketones and esters with second generation Pt(0) catalyst.

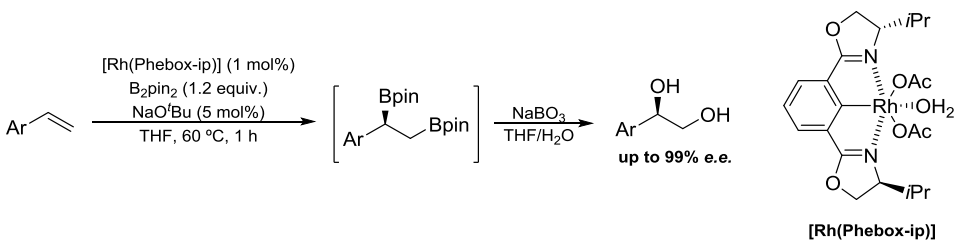
Kabalka and co-workers reported in 2002 the catalytic *β*-boration of a large scope of *a,β*-unsaturated carbonyl compounds (cyclic and acyclic ketones, esters, aldehydes and nitriles) using Wilkinson catalyst $[RhCl(PPh_3)_3]$.[49] Later on, these boronic acids were tested in boron neutron capture therapy.[50] This work solved some problems associated with the high catalyst loadings previously reported by Miyaura.[51] Thus, only 10 mol% of Wilkinson's catalyst was

required, compared to the stoichiometric copper catalyst loadings in the Miyaura's β-boration protocol. From the mechanistic point of view, it has been reported that diboron reagents can be added to Rh(I) and Pt(0) *via* oxidative addition, and the substrate could be coordinated to the metal center, to promote further Michael addition type 3,4-insertion and consequent boryl migration to the *β* position. From that point of view, two possible pathways could complete the catalytic cycle, depending on the nature of the substrate: direct reductive elimination to give the 3,4-diborated product, or tautomerization followed by the reductive elimination to give the 1,4-diborated product (Scheme 1.19).



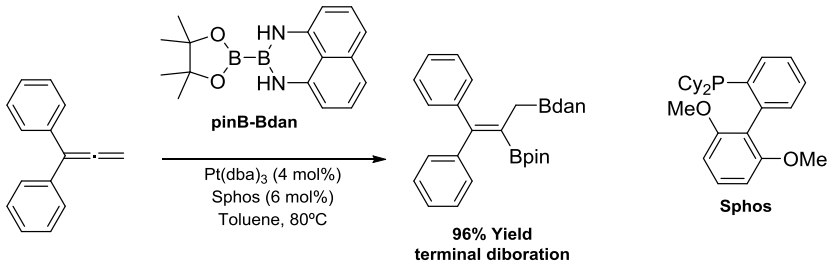
Scheme 1.19. Proposed catalytic cycle for the *β*-boration of activated alkenes.

In 2013 Nishiyama and co-workers reported a highly enantioselective diboration of terminal alkenes utilizing a chiral [Rh(Phebox-ip)] species and B_2pin_2. Through oxidation of the diboron adducts, they obtained optically active 1,2-diols in high yields and high enantioselectivities (Scheme 1.20).[52]



Scheme 1.20. Rh-catalyzed enantioselective diboration of alkenes.

Recently, Santos and co-workers have reported the Pt-catalyzed diboration of allenes with the mixed diboron pinB-Bdan. Remarkably, they have achieved a terminal diboration, contrarily to Miyaura's and Morken's previous works (Scheme 1.21).[53]



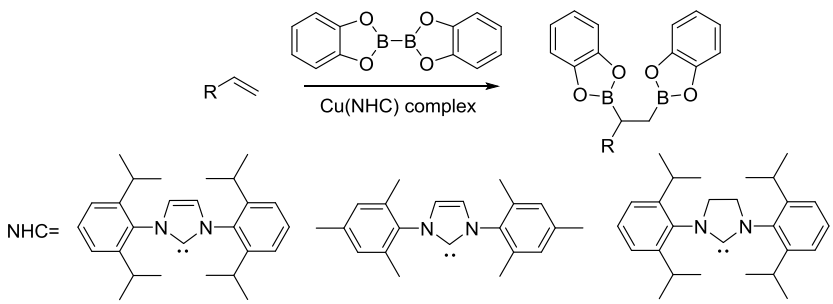
Scheme 1.21. Pt-catalyzed terminal diboration of allenes.

In 2007 our group reported a novel catalytic activation of the diboron reagent by palladium(II)-NHC complexes towards the chemoselective 1,2-diboration of alkenes. The presence of a mild base (NaOAc) and an excess of the diboron reagent are required, suggesting the heterolytic cleavage of diboron rather than oxidative addition of a B–B bond to the metal.

1.2.1.2 Activation *via* σ-bond metathesis

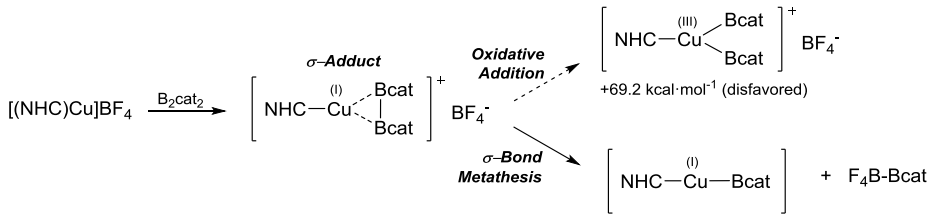
Usually, transition metals with lower *d* orbital energies fail in the activation of diboron reagents *via* oxidative addition, but some transition metal complexes react with tetralkoxydiboranes without changing the formal oxidation state of the metal and causing the heterolytic cleavage of the B-B bond. Therefore, in these cases the activation of the diboron reagent can be considered as σ-bond metathesis between the diboron reagent and the M-X unit (X= anionic ligand, alkoxide preferentially).

The first copper mediated diboration reaction was previously developed by our group. It was found that Cu(I) complexes modified with NHC (N-heterocyclic carbene) ligands activated bis(catecholato)diboron and promoted a selective addition to alkenes and alkynes with B_2cat_2 (Scheme 1.22). The B_2pin_2 reagent was found to be less efficient in this reaction.[54]



Scheme 1.22. Cu/NHC catalyzed first diboration of alkenes.

Theoretical Density Functional Theory (DFT) calculations were carried out in order to clarify the nature of the interaction between Cu/NHC complexes and B_2cat_2. The results were conclusive in favor of the formation of a sigma complex, and excluded the possibility of the oxidative addition due to the fact that its activation energy was 69.2 kcal·mol^{-1} higher than the sigma complex formation. The $[Cu(I)(NHC)(\sigma\text{-}B_2cat_2)]^+$ could further undergo a σ-bond metathesis to deliver the active Cu-boryl species (Scheme 1.23).[54]



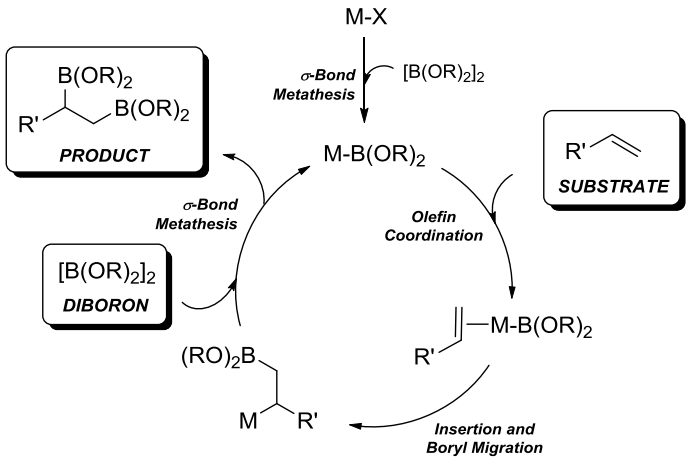
Scheme 1.23. Activation of B_2cat_2 with [Cu(NHC)](I) complexes via σ-bond metathesis.

Further DFT calculations reported by Marder and Lin pointed out the differences in reactivity between the two diboron reagents, B_2cat_2 and B_2pin_2.[55] Both metathesis reactions have similar and very small Gibbs free energy barriers ($\Delta G^{\neq}$= 6.5 kcal·mol^{-1} and 2.5 kcal·mol^{-1} respectively). However, the nature of the diboron reagent is again important in the activation pathway, as binding of B_2cat_2 appears to be much more favorable (ΔG= -15.6 kcal·mol^{-1}) than for B_2pin_2 (ΔG= -1.8 kcal·mol^{-1}), as a matter of the enhanced Lewis acid properties of the B_2cat_2.

Catalytic diboration of alkenes with transition metal complexes based on coinage metals (copper, silver and gold) was first explored by Marder and coworkers.[35] The catalytic system tested was [Au(PEt_3)Cl]/1,2-bis(dicyclohexylphosphino)ethane, because the gold system, as an example of metal

with lower *d* orbital energy, disfavors the *β*-hydride elimination pathway. The authors found that terminal alkenes could be chemoselectively transformed into the 1,2-diborated products, although high temperatures (80 ºC) and long reaction times (84 hours) were required.

The reaction mechanism might involve the heterolytic cleavage of the diboron reagent by σ-bond metathesis, leading to the formation of the boryl complex, subsequent alkene coordination, insertion and another σ-bond metathesis with the diboron reagent to provide the desirable product and regenerate the active species. The generation of the metal-boryl species was required to start the catalytic cycle (Scheme 1.24).



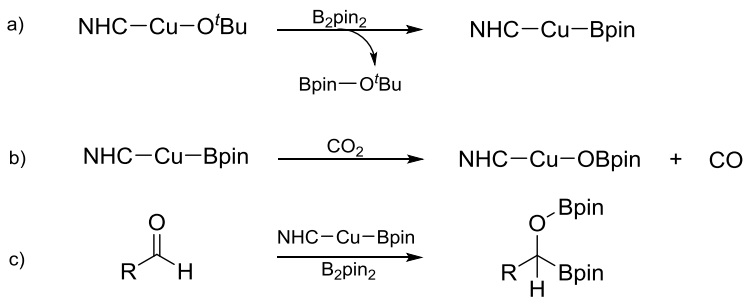
Scheme 1.24. Proposed catalytic cycle for the diboration reaction through σ-bond metathesis.

Our group was able to demonstrate that gold(0) nanoparticles stabilized with diphosphines were responsible for the diboration of alkenes, providing complete chemoselectivity towards the 1,2-bis(boronate)esters.[46] Of particular importance are the mild reaction conditions, the low catalyst loading and the substrate scope.

Alternative catalytic systems based on silver complexes modified with N-heterocyclic carbene ligands were also found to promote the chemoselective diboration of alkenes.[56]

In 2005, Sadighi and co-workers[57] reported the activation of diborons with Cu(I) salts, and the application of copper-boryl systems in boron addition reac-

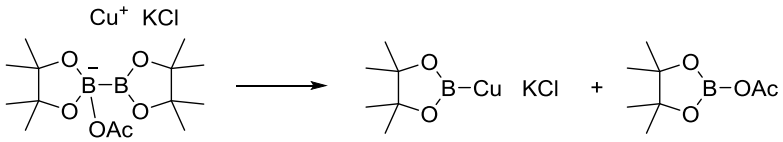
tions. The early approach by Sadighi and co-workers was the isolation of LCu-Bpin species (whereby L= N-heterocyclic carbene ligand) from LCu-O^{t}Bu and B_2pin_2 through σ-bond metathesis (Scheme 1.25, *path a*).[57a] Another important discovery by Sadighi's team involved the use of NHC-Cu-Bpin species in the reduction of CO_2 to CO (Scheme 1.25, *path b*), and the diboration of aldehydes (Scheme 1.25, *path c*).[57b]



Scheme 1.25. Sadighi and co-workers' approaches towards copper-boryl synthesis and applications.

The use of copper salts in borylation reactions became very popular. Thus, *β*-boration of *α,β*-unsaturated carbonyl substrates was explored by Miyaura and co-workers,[51] and Hosomi and co-workers,[58] at the same time but independently. They reported that Cu(I) salts in the presence of the suitable additives, catalyzed the *β*-boration of *α,β*-unsaturated ketones and esters. In both cases the products were obtained after the aqueous work-up, and the possible primary 1,4- or 3,4-diborated products were not observed.

Miyaura and co-workers used copper chloride as precursor and potassium acetate (KOAc) as additive. The authors were able to study that the base assisted the transmetallation between the CuCl and the B_2pin_2 by ^{1}H NMR spectroscopy (Scheme 1.26).

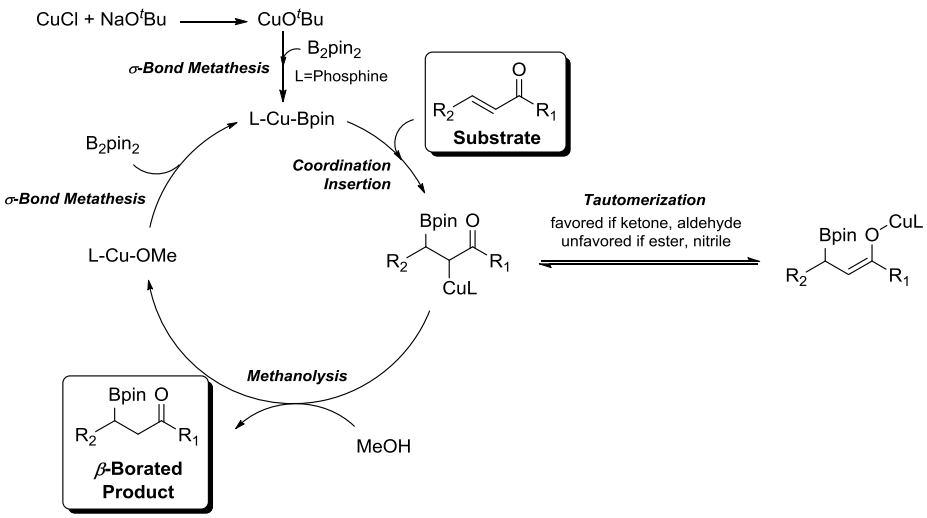


Scheme 1.26. Base assisted transmetallation between B_2pin_2 and CuCl.

Both systems were fairly efficient in the *β*-boration of *α,β*-unsaturated carbonyl compounds, even though long reaction times were required in order to obtain good yields. This drawback was overcome in 2006, when Yun and coworkers optimized the reaction conditions introducing MeOH as an additive to facilitate the recovery of the catalytically active species and provide a H^+ source for the formation of the desired *β*-borated product.[59] Apart from MeOH, other alcohols were also tested in order to accelerate the reaction and achieve complete conversions with alkenes[59] and alkynes,[60] at room temperature within short reaction times. The catalytic system consists on inexpensive copper chloride salt and a phosphine ligand, a catalytic amount of base (usually sodium *tert*-butoxide), a diboron reagent (B_2pin_2) and methanol.

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

Coordination of the substrate and Michael type migratory insertion of the Bpin moiety provided the 4-Bpin-3-copper-alkyl intermediate, which could form the copper-enolate intermediate by tautomerization. Methanolysis of both species provided the product and copper(I)-methoxide, which interacted with B_2pin_2 to regenerate the catalytically active species (Scheme 1.27).

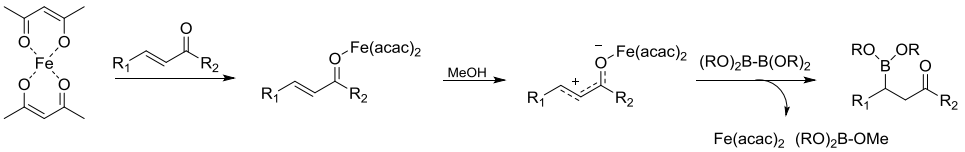


Scheme 1.27. Postulated catalytic cycle of the Cu-catalyzed *β*-boration of *α,β*-unsaturated carbonyl compounds.

However, the first successful approach to the enantioselective catalytic *β*-boration reaction was developed in 2006 by Yun and co-workers,[59] utilizing a chiral diphosphine that modified the copper-boryl catalytic system. After further optimization, the authors reported in 2008 that ferrocenyl type chiral diphosphines were very efficient to promote high values of enantioselectivity in the *β*-boration of *α,β*-unsaturated esters and nitriles (up to 94%).[61]

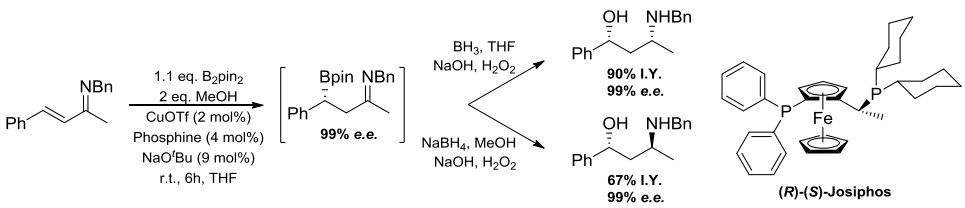
Also in 2008 Lin, Marder and co-workers carried out a comparative DFT study on the copper catalyzed *β*-boration of acrolein and methylacrylate.[62] They have shown that the model substrate, *α,β*-unsaturated aldehyde and ester, reacted with copper-boryl complexes through C=C insertion into the Cu-B bond, forming the corresponding Michael addition product. The aldehyde undergoes keto-enol tautomerization and forms the corresponding Cu-enolate, while in the case of the ester the tautomerization did not occur due to the inertness of the ester group.[55]

Lately, our group found out that iron(II) and (III) complexes can promote the *β*-boration reaction of a wide range of *α,β*-unsaturated carbonyl compounds.[63] In this case, a pre-activation of the substrate by the Lewis acidic Fe(II) and Fe(III) salts seems to have a beneficial influence on the reaction outcome (Scheme 1.28).



Scheme 1.28. Iron activation of the substrates in the *β*-boration reaction.

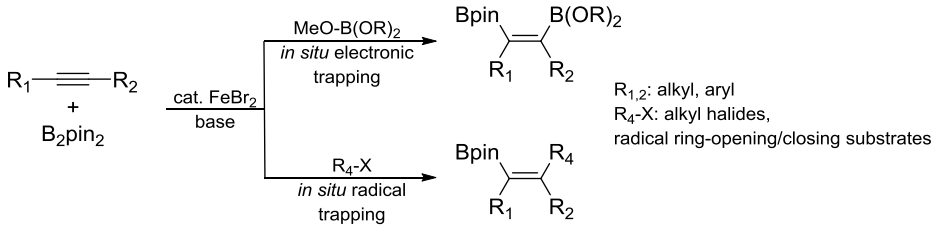
The same year, our group in collaboration with Whiting's group was able to achieve a highly enantio- and diastereo-selective synthesis of γ-amino alcohols from *α,β*-unsaturated imines through a one pot Cu(I) catalyzed *β*-boration / reduction / oxidation sequence (Scheme 1.29).[64] This methodology was also applied in the total synthesis of bioactive species.[64g]



Scheme 1.29. One pot synthesis of γ-amino alcohols.

In 2012, Santos and co-workers contributed to the field of copper mediated *β*-boration with a Cu(II) system, that is not oxygen sensitive and allowed the reaction to be carried out in water.[65]

Recently, Nakamura's group has successfully performed the first iron-catalyzed diboration and carboboration of alkynes, representing an outstanding advance due to the iron catalysts' lower cost.[66] By changing the MeO-B(OR)$_2$ additive, they have been able to obtain a number of mixed diborated products avoiding the arduous task of preparing the mixed diborons (Scheme 1.30).



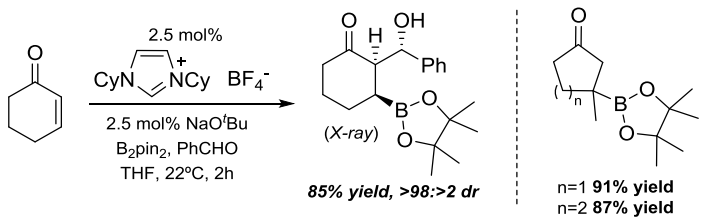
Scheme 1.30. Iron-catalyzed diboration and carboboration of alkynes.

In 2014 Sepúlveda-Escribano's group found out that platinum nanoparticles supported on titania efficiently catalyze the diboration of alkynes and alkenes under solvent- and ligand-free conditions in air. The *cis*-1,2-diborylalkenes and 1,2-diborylalkanes were obtained in moderate to excellent yields following, in most cases, a simple filtration workup protocol. The versatility of the *cis*-1,2-diborylalkene compounds was demonstrated in a series of organic transformations, including the Suzuki-Miyaura cross coupling and the boron-halogen exchange.[67]

1.2.2 Activation of diboron reagents by organocatalytic approaches. Applications

Intermolecular activation of symmetrical diborons such as B_2pin_2 can create a significant nucleophilic boryl synthon, which in the absence of any transition metal complexes can efficiently be transferred to the C_β of *a,β*-unsaturated carbonyl compounds. The so-called "pull-push effect" of B is understood as the quaternization of one B atom of the diboron forming an activated adduct which subsequently releases a boryl unit with enhanced nucleophilicity. This quaternization can be achieved by many ways.

Back in 2009, Hoveyda and co-workers reported the first metal-free system able to activate tetraalkoxydiborons towards the efficient C-B bond formation using 10 mol% of an imidazolium salt and equimolar amouts of sodium *tert*-butoxide (Scheme 1.31).[68] The authors postulated that the *in situ* generated nucleophilic N-heterocyclic carbene could interact with the Lewis acidic boron atoms of B_2pin_2 to activate the B-B bond.[68-69] Under this reaction conditions (Scheme 1.31), cyclic and acyclic *a,β*-unsaturated ketones or esters were *β*-borated in up to >98% yield. Remarkably, they also demonstrated that under those metal-free conditions, the reactivity and site-selectivity levels were comparable to the use of a Cu-catalyzed system.

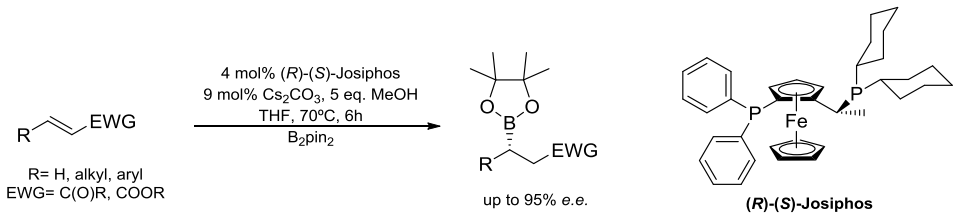


Scheme 1.31. Representative scheme of the reaction conditions for the metal-free *β*-boration reaction reported by Hoveyda and co-workers.

Importantly, by means of spectroscopic and DFT studies, Marder and co-workers later on 2011 demonstrated the existence of a neutral Lewis acid-base adduct of B_2pin_2 and an N-heterocyclic carbene (NHC) both in solution and in the solid state.[70] They observed that the B-carbene binding was weak in solution and NMR spectroscopy revealed a rapid exchange of the NHC between the two boron centers. DFT calculations demonstrated that the exchange involved

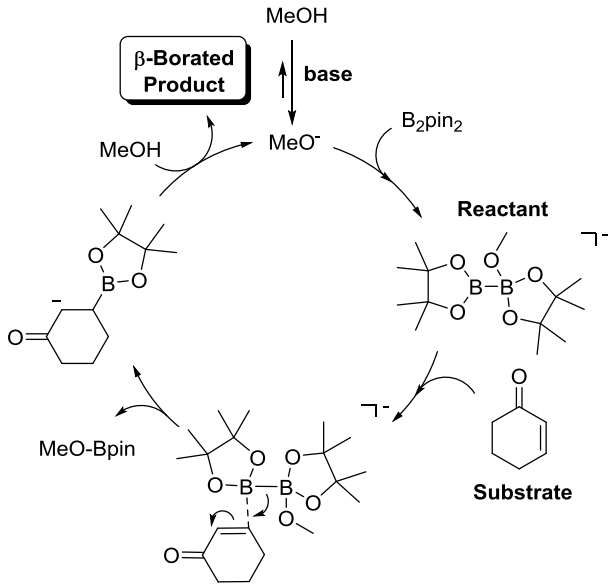
dissociation and re-association of the NHC rather than an intramolecular process.

In this context, our group successfully developed the first asymmetric organocatalytic *β*-boration reaction based on the use of a Brönsted base, methanol and chiral phosphines in the presence of B_2pin_2.[71] By employing the suitable phosphine, high conversions and high levels of enantioselection could be obtained for a wide range of *α,β*-unsaturated carbonyl compounds (Scheme 1.32).[71] Both inorganic and organic bases deprotonated MeOH and the resulting methoxide formed a Lewis acid-base adduct with the diboron reagents. Other similar adducts have also been reported by Kleeberg and Marder.[72]



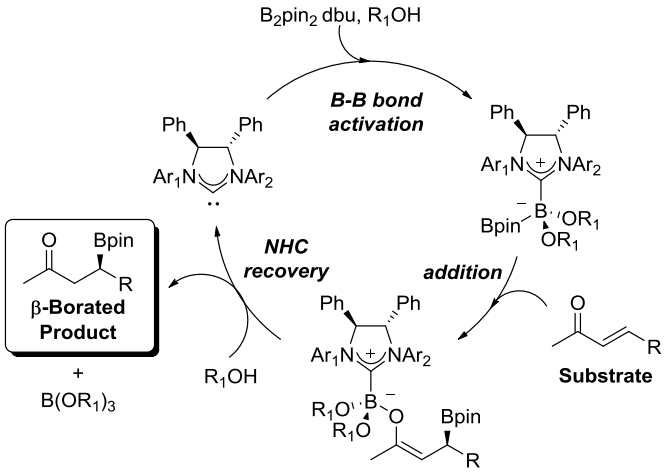
Scheme 1.32. General scheme for the first asymmetric metal-free *β*-boration reaction.

During this process, the sp^2 boron of the $[B_2pin_2 \cdot MeO^-]$ adduct gained a pronounced nucleophilic character and attacked the electron deficient olefins. The frontier orbitals that are involved in the attack that leads to the transition state are the polarized σ-B-B bond and the π*C=C of the activated olefin. From the transition state the anionic organic intermediate is formed directly *via* the heterolytic cleavage of the B sp^2-B sp^3 bond and the formation of the new C-B bond. Protonation of the anionic intermediate with MeOH provided the product and generated another methoxide anion, converting the reaction into a catalytic process (Scheme 1.33). The efficiency of the catalytic system has been found to depend on the nature of the base that is used to deprotonate the MeOH. It has been observed that the organic Verkade base is able to promote quantitatively the MeO^- formation to consequently activate diborons such as B_2pin_2, B_2cat_2, B_2hex_2, and B_2neop_2.[73]



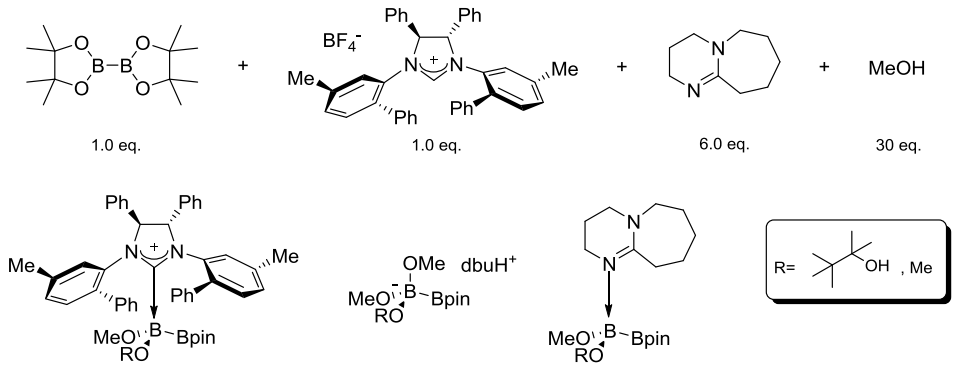
Scheme 1.33. Proposed catalytic cycle for the methoxide-mediated metal-free *β*-boration of *α,β*-unsaturated compounds with B_2pin_2.

Later on, Hoveyda and co-workers reported the asymmetric version of the organocatalytic *β*-boration utilizing chiral NHC.[74] Using 7.5 mol% of imidazolium salt, 30 mol% of dbu (1,8-Diazabicyclo [5.4.0]undec-7-ene.), 60 eq of MeOH the authors were able to perform the *β*-boration of a series of *α,β*-unsaturated compounds with relatively high levels of enantioinduction in a range of 22-50 ºC. Even though the addition of MeOH was crucial for an active system, the authors suggested that the NHC activates the diboron reagent by a Lewis acid-base adduct (Scheme 1.34).



Scheme 1.34. Mechanistic proposal for the NHC-mediated enantioselective metal-free *β*-boration reaction.[74]

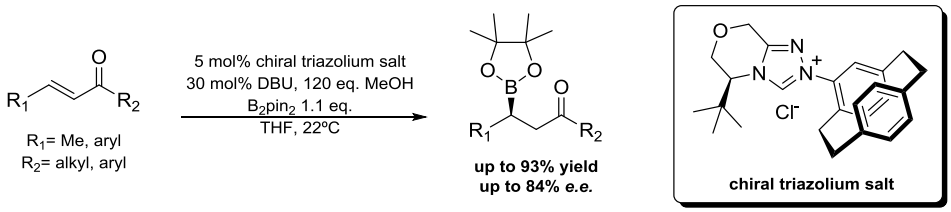
Recently, the same author performed an exhaustive study by means of NMR and DFT to justify the role of each reagent in the reaction and explain the different observed behavior of the chiral and non-chiral NHC.[75] Hoveyda justifies the need of a huge excess of base and methanol to the methanolysis and subsequent formation of less hindered boryl species that allow a better B-NHC coordination, as well as a number of species such as base-B_2pin_2 adduct (Scheme 1.35). He also discards other possible pathways such as the pre-activation of the substrate by the carbene or a radical-based mechanism.



Scheme 1.35. Hoveyda's reported relevant species formed in the NHC reaction with B_2pin_2 in the presence of an excess of methanol and dbu.

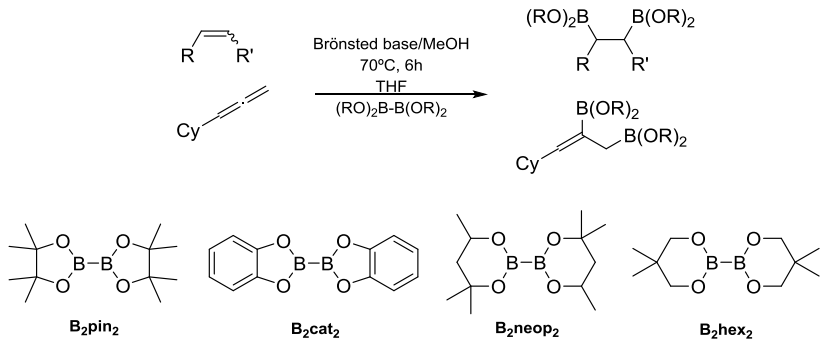
Also this year, Ma and co-workers[76] following the same line, reported an enantioselective conjugate addition of boron to *α,β*-unsaturated ketones cata-

lyzed by either a NHC or a copper–carbene complex generated *in situ* from a new chiral bicyclic triazolium salt. Both approaches afford a number of chiral β-boryl ketones in good yields and enantioselectivities although the dual chiral NHC–Cu catalyst presents significant advantages over the organocatalytic process (Scheme 1.36).

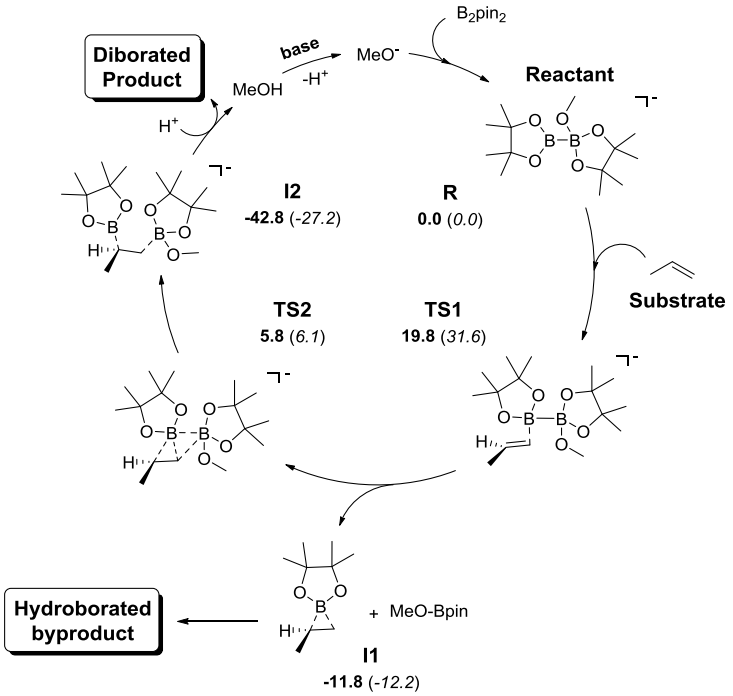


Scheme 1.36. Enantioselective boron conjugate addition catalyzed by a chiral NHC.

In 2011, our group was able to conduct the first successful metal-free diboration reaction of non-activated olefins and allenes (Scheme 1.37).[77] Remarkably, the diboration was achieved using a number of diboron reagents and substrates. The reaction mechanism was also unraveled by means of DFT methods. Interestingly, a transition state is directly connected to another one lower in energy (Scheme 1.38).[77] This phenomena was reported in 2008 by Houk and co-workers and it is known as bifurcation.[78]

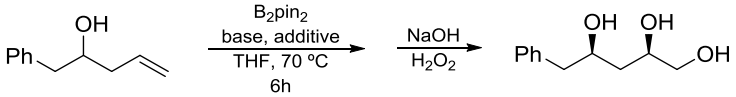


Scheme 1.37. Transition metal-free diboration of alkenes and allenes.



Scheme 1.38. Proposed mechanism for the organocatalytic diboration reaction. Electronic energy and Gibbs free energy (in parentheses) computed at M06 level relative to the adduct $[MeO{\cdot}B_2pin_2]^-$ plus propylene. All energies are in kcal·mol^{-1}.[77]

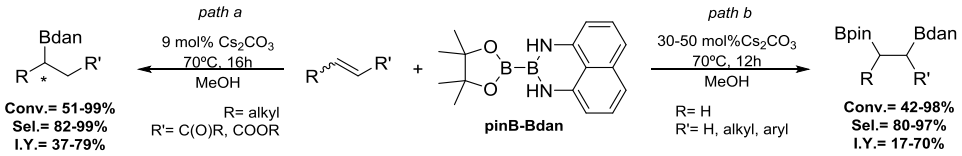
In 2014 Morken and co-workers reported an alkoxide-catalyzed directed diboration of alkenyl alcohols. This reaction occurs in a stereoselective fashion and its scope includes cyclic and acyclic homoallylic and bishomoallylic alcohol substrates. After oxidation, the reaction generates 1,2-diols, representing a method for the stereoselective directed dihydroxylation of alkenes (Scheme 1.39). Remarkably, this process can be performed at >5 g scale and at open air flasks.[79]



Scheme 1.39. Organocatalytic hydroxyl-directed stereoselective diboration of alkenes.

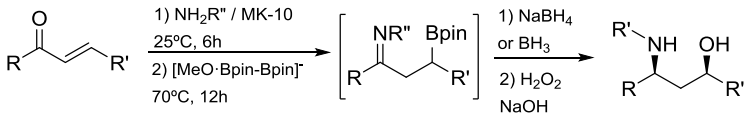
During the following years, our group has gained even more expertise in the field of organocatalysis, being able to achieve the first examples of metal-free *β*-boration[80] and diboration[81] reactions with the mixed diboron "pinB-Bdan" (Scheme 1.40). Interestingly, in the *β*-boration reaction, the Bdan moiety is preferably transferred to the substrate. This fact was also rationalized by DFT

studies.[80] Also, in the 1,2-diboration reaction, the Bdan is first transferred to the substrate and after the rearrangement and the second boryl attack, the Bdan moiety remains in the internal position.[81]



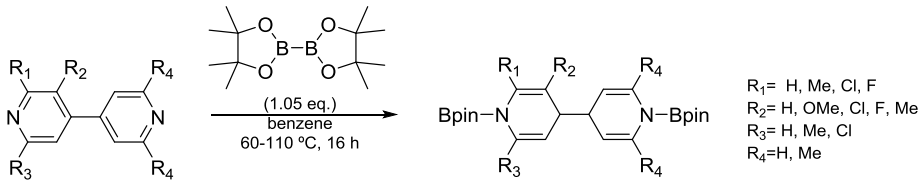
Scheme 1.40. Reaction of alkenes with the mixed diboron reagent pinB-Bdan.

More recently, the unprecedented enantioselective *β*-boration of *in situ* generated imines was successfully performed in our group (Scheme 1.41).[82] Subsequent reduction and oxidation reactions were performed towards the formation of the corresponing γ-amino alcohols. DFT studies showed that the activation energies for the *β*-boration of imines are higher than for the ketones, esters and aldehydes.[73]



Scheme 1.41. *In situ* formation of *β*-borylated imines and subsequent reduction and oxidation protocol.

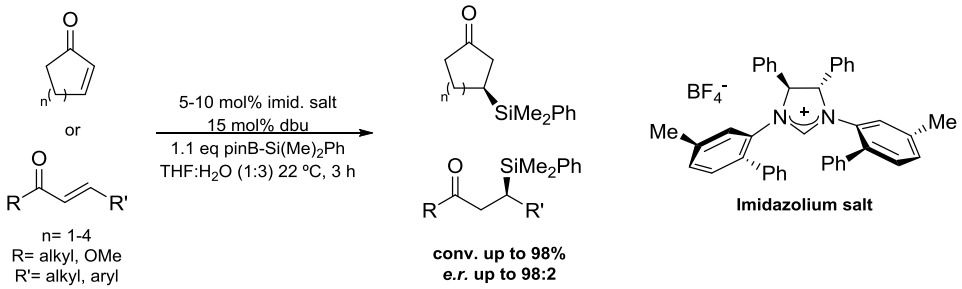
Early this year, Suginome and co-workers have reported the organocatalytic diboration using 4,4'-bipyridine species. They mention that a "reductive addition" of the B-B (σ-bond) occurs, due to the reduction of the organocatalyst that takes place. They have isolated the bypiridine catalytic species and have successfully achieved the diboration of a number of pyrazines (Scheme 1.42).[83]



Scheme 1.42. Organocatalytic diboration of pyrazines.

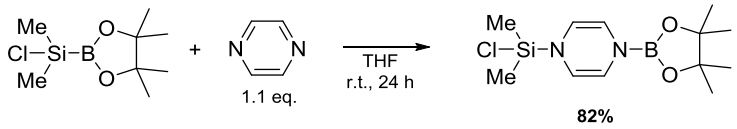
1.3 The *pull-push* effect of B on B-Y containing reagents

As explained above, quaternization of one boron atom in species containing B-B and B-Y bonds (Y= elements from group 14) induces the heterolytic cleavage of these stable bonds. The *pull-push* effect of B has also been studied with silanoboranes, enabling the introduction of nucleophilic silyl moieties by forming the Lewis acid-base adducts [Nu-B(OR)$_2$-SiMe$_2$Ph]. In the first example reported in 2011 by Hoveyda and co-workers, the authors were able to enantioselectively obtain a number of *β*-silylated ketones utilizing chiral imidazolium salts in a mixture of THF and H_2O (Scheme 1.43).[84]



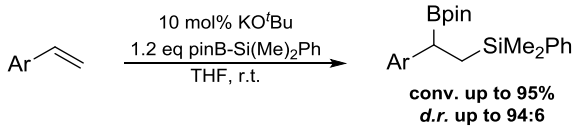
Scheme 1.43. Hoveyda's enantioselective *β*-silylation of *α,β*-unsaturated ketones.

Next year, Suginome and co-workers performed a transition metal-free diboration, silaboration and hydroboration of a number of pyrazines (Scheme 1.44).[85]



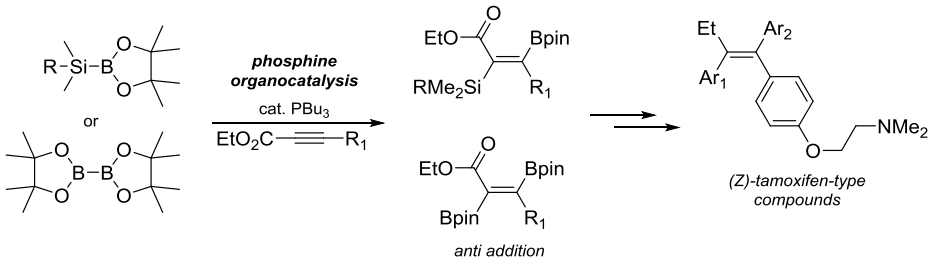
Scheme 1.44. Metal-free silaboration of pyrazines.

Also in 2012, Yamamoto and co-workers reported the potassium tert-butoxide-mediated regioselective silaboration of aromatic alkenes. The reaction proceeded in a highly regioselective manner, with only a single regioisomer being detected. Only a loading of 10% of the base was needed to achieve up to 99% yield (Scheme 1.45). Interestingly, they were also able to observe the activated adduct [^{t}BuO·Bpin-SiMe$_2$Ph]$^-$ by ^{11}B NMR (δ= 3.9 ppm).[86]



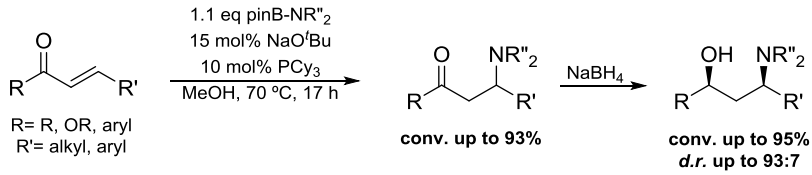
Scheme 1.45. Metal-free silaboration of aromatic alkenes.

Early this year, Sawamura and co-workers have reported an *anti*-selective vicinal silaboration and diboration of a number of alkynoates through phosphine organocatalysis. Further reactions afforded a family of (*Z*)-tamoxifen-type of compounds (Scheme 1.46).[87]



Scheme 1.46. Organocatalytic selective silaboration and diboration of alkynoates.

Our group has also studied the metal-free activation of aminoboranes through the same sort of adducts [Nu-B(OR)$_2$-NR'$_2$] and their reaction with *α,β*-unsaturated carbonyl compounds. In addition, a further reduction with NaBH$_4$ yielded the corresponding *γ*-amino alcohols with a good *syn* selectivity (Scheme 1.47).[88]



Scheme 1.47. Metal-free aminoboration of *α,β*-unsaturated carbonyl compounds and subsequent reduction towards the *γ*-amino alcohols.

1.4 Computational studies in the field of catalysis

The continuous advances and improvement of the computational methods during the past years has led the comprehension of chemistry to the next level, becoming nowadays an indispensable tool to understand many chemical processes. In particular, computational chemistry has been very successful in catalysis. Its potential arises from the capability of determining reaction mechanisms with suitable accuracy in a reasonable time, and accordingly understanding and often predicting the behavior of catalytic systems.

On the other hand, computational chemistry needs to be understood as a complementary tool of experimental chemistry. Thus, a comparison of obtained experimental and theoretical results leads to a better reaction comprehension. It is also worthy to mention that the choice of the computational method is crucial in the obtaining of coherent results. The main objectives of any modeling technique are to reproduce the experimental values and to identify and rationalize the catalytic process in order to obtain a mechanistic comprehension. The importance of computational chemistry in catalysis was reflected in the 2013 Nobel Prize in Chemistry, awarded to Martin Karplus, Michael Levitt and Arieh Warshel "*for their contribution in the development of multiscale models for complex chemical systems*".[89]

In homogeneous catalysis the computational strategy most frequently used is based in determining the key transition states (TS) using electronic structure methods, and it is frequently referred to *TS-based* approach. This approach requires the determination of the geometries and the energies of the reactants, products and all relevant intermediates and transition states of the reaction. This can be achieved through the localization of stationary points of the *potential energy surface* (PES) and their energy evaluation. Optimization of the geometries is usually done through gradient techniques. In this procedure, all degrees of freedom are varied simultaneously until the gradient (first derivatives) of the energy is zero. The characterization of the stationary points involves the differentiation between the local minima (intermediates, reactants and products) and saddle points (transition states), by computing the matrix of the second derivatives of the energy with respect to molecular coordinates (Hessian matrix). In the case of local minima all the eigenvalues or the Hessian matrix are positive, whereas in the saddle points, there is one and only one

negative *eigenvalue*. Based on this information, it is possible to identify the energy of each one of the involved species and determine the activity- and the selectivity-determining step of the catalytic cycle.

In this regard, Density Functional Theory (DFT) provides a suitable and time-economic way to handle a huge diversity of chemical systems. Such methods were developed based on the Thomas-Fermi-Dirac model (1920's) and on the work of Slater in quantum chemistry (1950's). Due to their importance, their authors Walter Kohn and John A. Pople were awarded with the Nobel Prize in Chemistry 1998 *"for his development of the density-functional theory"* and *"for his development of computational methods in quantum chemistry"* respectively.[90] DFT methods are similar to *ab initio* methods at a much less computational cost: they require approximately the same amount of computation resources as Hartree-Fock theory, the least costly *ab initio* method.

Density Functional Theory methods rely on the electron density rather than the wave function. This simplification is possible thanks to the development of the Hohenberg & Kohn theorem,[91] which states that all-ground state properties of a system are functions of the electron density. A functional is described as a function of a function, but the theorem does not provide the form of such functional. The most common implementation is the Kohn-Sham formalism,[92] which allows optimizing the energy by solving a set of one-electron equations, the so-called Kohn-Sham equations which are equivalent to Hartree-Fock equations.

The derived one-electron functions, the Kohn-Sham orbitals, can be also expressed as a linear combination of atomic orbitals. One of the main advantages of DFT methods is that they include electron correlation with a little computational cost compared to wavefunction-based methods. This term, *electron correlation*, referring to instantaneous repulsive interactions, is absent in Hartree-Fock theory. In the framework of wavefunction-based methods, electron correlation has to be introduced through computationally demanding schemes as configuration interaction or perturbation-methods.

The accuracy of a DFT calculation strongly depends on the quality of the exchange-correlation functional. As the exact expression of this functional is not known, some approximations are therefore needed. The quest for more accu-

rate DFT functional consists of variations and improvements on how to address this term. This is done nowadays by following two main approaches:

- From the theoretical physics side: Developing mathematical equations that allow the development of new functionals.
- From the computational chemists side: Fitting combinations of functionals to experimental data, which creates new methods.

The first DFT approximation was the local density approximation (LDA) where the functional depended only on the value of the electron density. It assumed that the charge varies slowly throughout the molecule so that the density can be treated as an uniform electron gas. The LDA approximation generally gives good results for the determination of structural features of the system, as well as for vibrational frequencies and dipole moments. However, it usually overestimates the binding energies.

Local spin-density approximation (LSDA) also includes electron spin. These functionals were good for solid state physics, but failed when calculating chemical properties. This was significantly improved by adding gradient corrections to the exchange correlation functional, through terms that involve the gradient of the density. It has been proposed several functionals belonging to this class of methods, named generalized gradient approximation (GGA). GGA methods take into account the fact that the electron density varies through the space, and as such, the approximation is more complex than that of the LDA method. GGA functionals typically estimate the energy of the systems with a reasonable accuracy, improving the results obtained with LDA functionals. Their performance is however limited in a number of cases, for instance when accurate description of van der Waals interactions is needed.[93]

Among the numerous functionals following the GGA approximation, BP86,[94] and BLYP[94a, 95] have been widely used. The accuracy of this functional can be improved by using higher level DFT meta-GGA approaches, in which the gradient of the density and its Laplacian (second derivative) are included too.

Another popular class of functionals is the hybrid-GGA, which combines the exchange-correlation term of the GGA approximation with a part of the exact Hartree-Fock exchange term. These functionals are now widely used because of the significant improvement obtained for the description of a wide range of

molecular properties. Probably, the most popular hybrid is the B3LYP scheme.[95-96] It owes its origins to a proposal by Becke for a parameterized hybrid approximation involving the Perdew correlation functional,[97] which lately was substituted by the LYP correlation functional.[95, 98]

More recently, Truhlar and co-workers have developed a suit of meta-hybrid density functionals including M06, M06-HF, M06-2X, M05 and M05-2X.[99] Meta-hybrid-GGA functionals are increasingly used in chemical modeling, since some of them appear to describe accurately molecular systems containing weak interactions (such as van der Waals interactions).

A good alternative is the use of DFT methods that include dispersion correction (DFT-D) such as B97D,[100] B97D3[101] or wB97XD.[102]

The more complex functionals (developed through a more complex approximation) describe more precisely the electron density, and by extension provide more accurate descriptions of the molecular properties as it is represented by the Jacob's ladder of exchange-correlation functionals (Figure 1.4).[103]

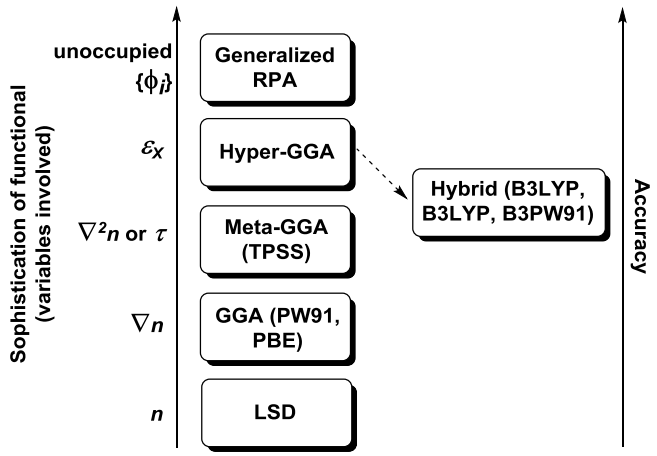


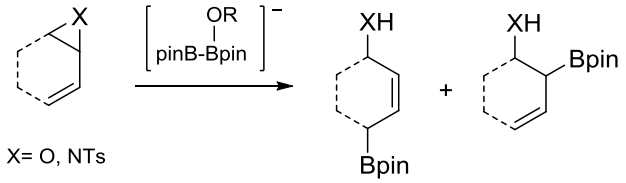
Figure 1.4. Jacob's ladder of exchange-correlation functionals.

As it has been explained above, the choice of a particular method compromises the quality of the results and the time spent for the calculation. In this PhD thesis, various functional have been used, mainly the meta-hybrid M06-2X, the GGA BP86, and occasionally the hybrid B3LYP.

1.5 Objectives of the thesis

The quaternization of a boron atom in B-B and B-Y bonds serves as a platform to introduce a nucleophilic moiety into unsaturated molecules. This thesis focuses in the so-called *pull-push* effect of B on B-B and B-Y (Y= S, Se) containing reagents to selectively introduce nucleophiles on different sort of substrates. Thus, these are the objectives of the thesis:

Objective 1: The use of the Lewis acid-base diboron adducts to undergo a borylative ring opening of vinyl epoxides and aziridines. In addition, the development of DFT studies in order to complete the understanding of this approach (Scheme 1.48).

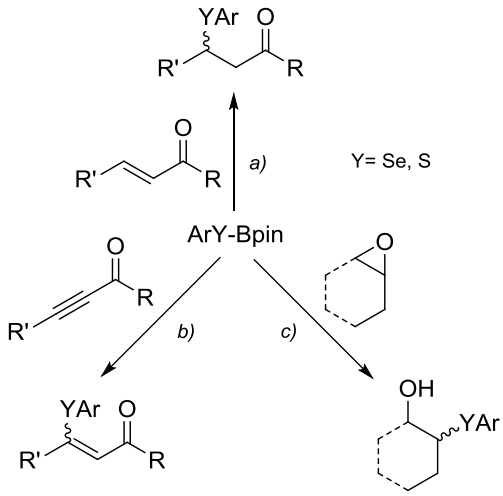


Scheme 1.48. Metal-free borylative ring opening of vinyl epoxides and aziridines.

Objective 2: The study of the synthesis of *β*-seleno and *β*-sulfido carbonyl compounds through the addition of a novel B-Se and B-S reagents to enones. The deep understanding of the plausible mechanism and reactivity by means of computational studies (Scheme 1.49, a).

Objective 3: To tackle from a theoretical point of view the selenoboration and thioboration of propargyl ketones and compare the obtained results to our group's experimental results to complete the understanding of the reaction (Scheme 1.49, b).

Objective 4: To explore experimentally the epoxide interaction with the novel B-Se and B-S reagents to promote the ring opening, in a metal-free context, and obtain *β*-hydroxy selenides and sulfides (Scheme 1.49, c).



Scheme 1.49. Metal-free reaction of the ArY-Bpin reagents with different substrates.

1.6 References

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"Nothing in life is to be feared,
it is only to be understood.
Now is the time to understand more,
so that we may fear less."

Marie Curie

2. Metal-free borylative ring opening of vinyl epoxides and aziridines

Table of contents

UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

2.1 Introduction

2.1.1 Vinyl epoxides and aziridines. Use and main reactivity

Vinyl epoxides are versatile organic substrates because of their wide reactivity with different reagents.[1] The strained oxirane ring is already a reactive moiety by itself and joint with the presence of a conjugated double bond the molecule exhibits a unique reactivity that is not observed by the two of them separately. Of great interest is their reactivity with nucleophiles called "nucleophilic opening" reaction and this reaction has been observed at all four electrophilic reactive sites (Figure 2.1). Generally, soft nucleophiles tend to attack vinyl epoxides *via* an S_N2' process (Figure 2.1, pathway a), while hard nucleophiles prefer the S_N2 attack (Figure 2.1, pathway b).[2] Attack *via* pathway c is an alternative S_N2 attack that occurs when this reaction site is particularly unhindered compared to attack *via* pathway b, or if the nucleophile is internal and the ring size disfavors pathway b, or when there are directing groups. Nucleophilic addition *via* pathway d has been observed only for the substrates where R is an electron-withdrawing group that competes with the reactivity of the epoxide.

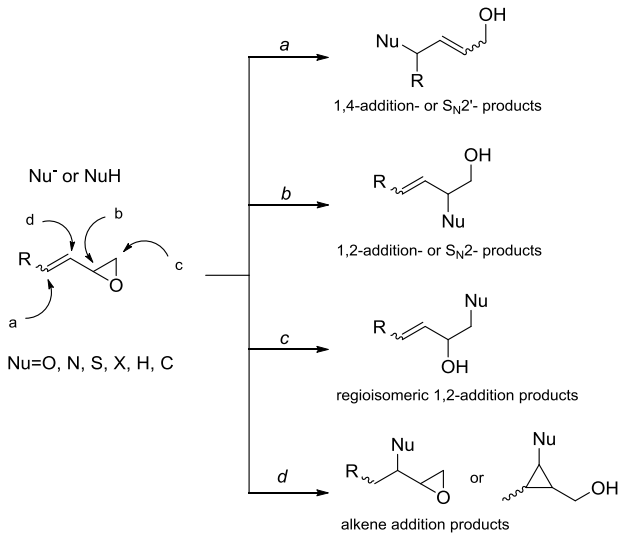
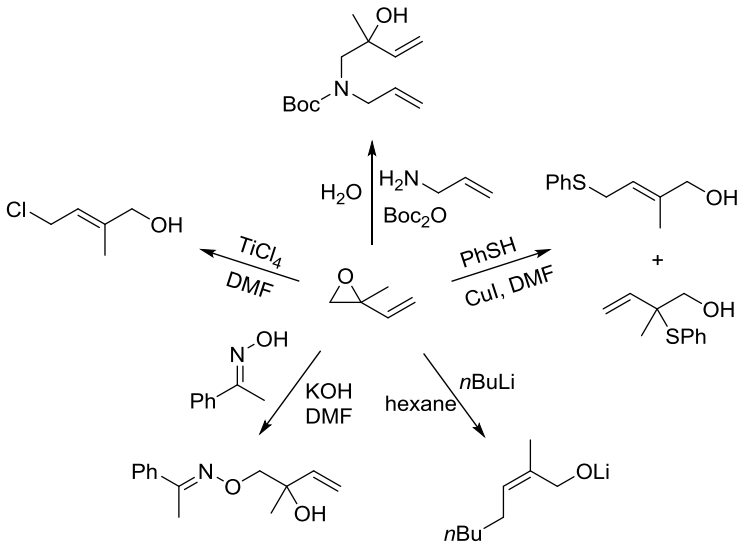


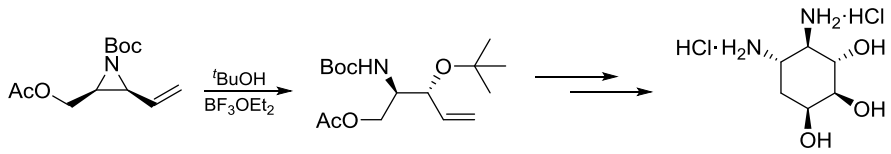
Figure 2.1. Nucleophilic ring-opening pathways of vinyl epoxides.

This reaction can be performed with different sorts of nucleophiles such as nitrogen nucleophiles,[3] oxygen nucleophiles,[4] sulfur nucleophiles,[5] halide nucleophiles,[6] carbon nucleophiles[7] and other nucleophiles (Scheme 2.1).[1]



Scheme 2.1. Several examples of nucleophilic attack to vinyl epoxides.

On the other hand, vinyl aziridines are a kind of substrates that present a very similar chemical behavior to vinyl epoxides. They have been used as key intermediates in the synthesis of diverse nitrogen-containing natural products. The nucleophilic ring opening reaction is also the most useful transformation of the vinyl aziridines towards complex organic molecules (Scheme 2.2).[8] However, the nucleophilic ring opening of vinyl aziridines has been less explored than the same reaction for epoxides.

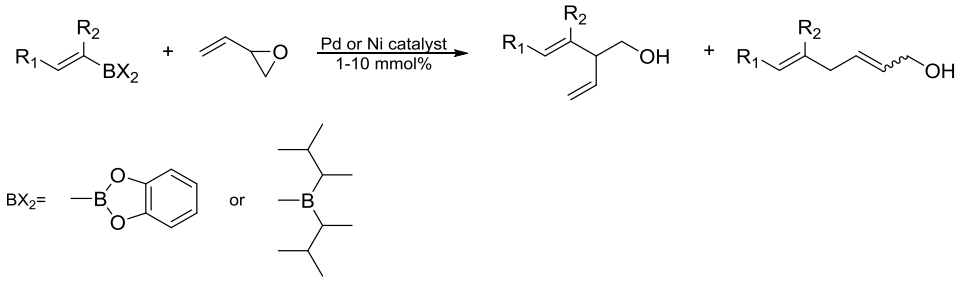


Scheme 2.2. Nucleophilic ring opening of a vinyl aziridine in organic synthesis.

Despite the fact that boron compounds are well-known for their Lewis acidity and their electrophilic character, they can also act as nucleophiles, as it has been widely explained in the first chapter. Hence, regarding boron nucleophiles, the borylative ring opening reaction of vinyl epoxides and aziridines has been explored during the past years.

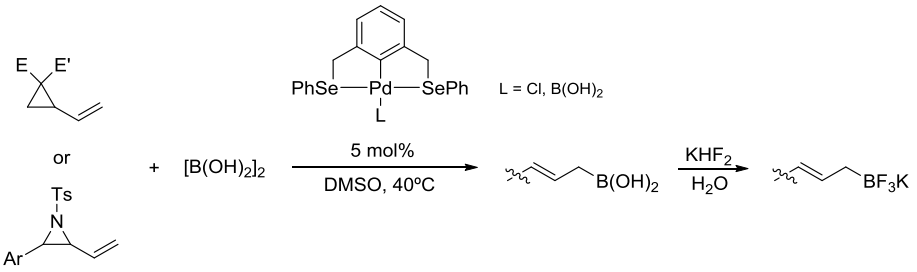
2.1.2 Borylative Ring Opening reaction

The use of organoboronic compounds as mild carbon nucleophiles for the ring opening reaction remains limited to particular classes of epoxides and aziridines. In a seminal paper in 1982, Suzuki and Miyaura reported a cross-coupling of 1-alkenylboranes with 1,3-butadiene monoepoxide catalyzed by nickel or palladium complexes, which occurs with in some cases high regioselectivity (Scheme 2.3). Interestingly, the ratio of the two dienols can be reversed by changing the metal complex.[9]



Scheme 2.3. Palladium and nickel catalyzed first example of cross-coupling between organoboron compounds and vinyl epoxides.

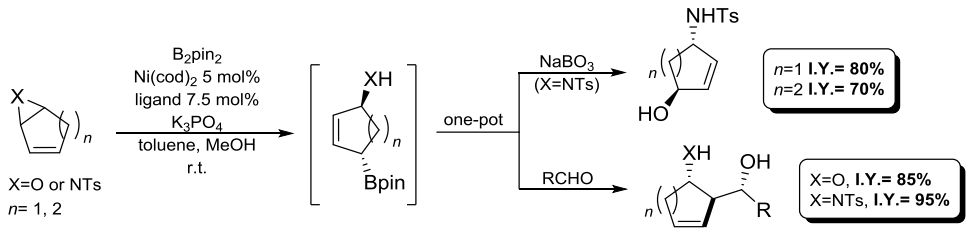
The first approach to the borylative ring opening reaction was described in 2005 by Szabó and co-workers[10] who reported the borylation of vinyl cyclopropanes and aziridines using palladium pincer complexes. This process is a S_N2' reaction where the nucleophilic boron moiety attacks to the double bond causing the subsequent ring opening. Afterwards, the authors transformed the allyl boronate species into potassium trifluoro(allyl)borates (Scheme 2.4).



Scheme 2.4. Borylative ring opening of vinyl cyclopropanes, aziridines and allylacetates catalyzed by palladium pincer complexes.

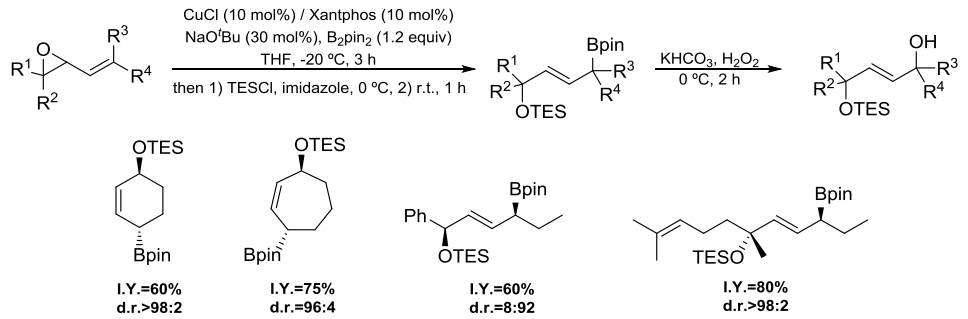
The borylation of vinyl epoxides was reported in 2009 by Pineschi and co-workers utilizing $Ni(cod)_2$ as catalyst. Addition of B_2pin_2 to cyclic vinyl epoxides

and aziridines occurred stereoselectively in an *anti*-SN_2' fashion.[11] The borylated product was unstable to chromatographic column but reacted *in situ* with benzaldehyde to afford 1,3-diols containing three contiguous stereocenters in high yields and excellent selectivity (Scheme 2.5). Acyclic vinyl epoxides, such as butadiene monoxide and isoprene oxide, were also examined under the same conditions. However, although the reaction proceeded, the selectivity was poor in those cases.



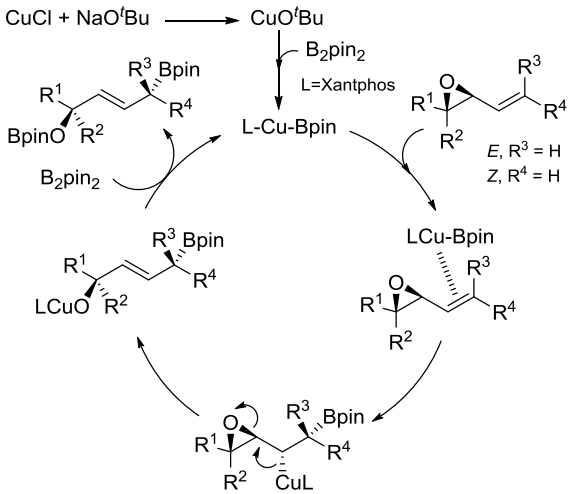
Scheme 2.5. Nickel catalyzed borylative ring opening of cyclic vinyl epoxides and tosylaziridines.

Tortosa later on 2011 reported a copper(I) catalyzed selective *syn* and *anti* 1,4-diol formation afforded by the proper choice of the double bond and oxirane geometries. This process starts with the CuCl/Xantphos catalyzed addition of B_2pin_2 to vinyl epoxides and the formation of the corresponding boronates and the subsequent *in situ* oxidation with alkaline H_2O_2 (Scheme 2.6).[12] Moderate to very good yields of 1,4-diols were obtained with good diastereoselectivity. Alternatively, it is possible to *in situ* protect the allyl borate before the oxidation. In this manner, monoprotected 1,4-diols could be isolated in 60−80% yields. In addition, cyclic derivatives could be obtained in 60−75% yields with excellent diastereoselectivity from cyclic vinyl epoxides.



Scheme 2.6. Cu(I) catalyzed borylative ring opening of vinyl epoxides and subsequent alcohol formation.

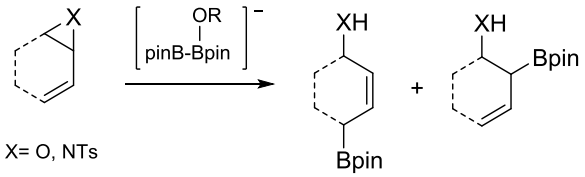
The proposed catalytic cycle starts with the reaction of the copper salt with the base *via* transmetalation to form the CuO^{t}Bu species which undergoes a σ-bond metathesis with a B_2pin_2 molecule and coordinating a Xantphos ligand forming the active species L-Cu-Bpin. This bisphosphine−copper−boron complex coordinates to the double bond of the vinyl epoxide *anti* with respect to the stereochemistry of the epoxide. Then a 1,2-insertion occurs followed by an elimination with the epoxide ring opening to form the copper alkoxide species. This species finally proceeds to another σ-bond metathesis with B_2pin_2 regenerating the active species L-Cu-Bpin and completing the catalytic cycle (Scheme 2.7).



Scheme 2.7. Proposed mechanism of the copper(I) catalyzed borylative ring opening of vinyl epoxides.

2.2 Motivation

Since all the previously reported borylative ring opening reactions took place in the presence of transition metal catalysts (Pd, Ni or Cu)[13] our aim was to promote the same reaction in absence of any transition metal. To do so, and based on our previously developed protocols in the field of the metal-free diboron activation by simple alkoxides;[14] we focused our efforts to study the transfer of a nucleophilic boryl unit[15] from an *in situ* formed $[MeO{\cdot}B_2pin_2]^-$ adduct,[14i, 16] to vinyl epoxides and vinyl aziridines (Scheme 2.8).



Scheme 2.8. Predicted reaction of vinyl epoxides and aziridines with the activated $[MeO{\cdot}B_2pin_2]^-$ adduct.

Moreover, our aims also included the identification, isolation and the characterization of the borylated products, as well as their derivatized products.

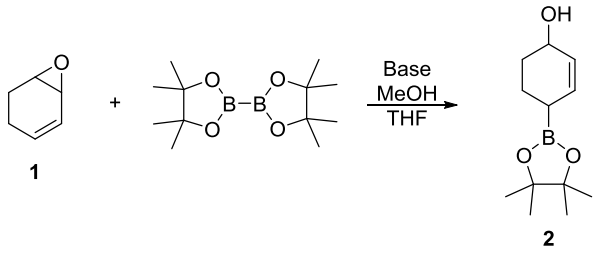
At the same time we wanted to perform DFT studies in order to explain and predict the experimental results and to propose a plausible mechanism. As the activation of the B_2pin_2 reagent has been previously theoretically well studied in our group,[14i] we wanted to explore the reactivity of this activated adduct when interacting with this sort of substrates.

2.3 Results and discussion

2.3.1 Experimental results

We considered first a reaction of the model epoxide substrate 3,4-epoxy-1-cyclohexene (**1**) with B_2pin_2 in THF. As expected, no conversion of the substrate was observed since the diboron reagent was not activated. However, the addition of a catalytic amount of base such as Cs_2CO_3 and MeOH favored the activation of the diboron by the formation of the Lewis acid-base adduct $[B_2pin_2{\cdot}OMe]^-$, and after 6 hours of reaction at room temperature, a new organoboron product was observed.

The reaction was followed by ^1H NMR spectroscopy, and it was possible to observe the appearance of two new coupled signals at 5.6 and 5.7 ppm that correspond to two different olefinic protons. Also, a new peak in the ^{11}B NMR at 33.8 ppm was observed, confirming the presence of a borylated product. We suggested that the nucleophilic pinacolboryl unit exclusively attacked the double bond providing the 4-pinacolboryl-2-cyclohexen-1-ol (**2**) species *via* a S_N2' pathway. Remarkably, this single product was exclusively obtained (Scheme 2.9).



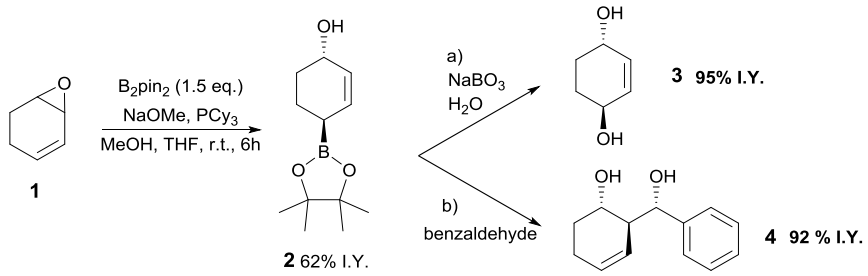
Scheme 2.9. Observed reactivity of the model vinyl epoxide **1** with B_2pin_2.

After screening a number of bases and solvents we realized that a 20 mol% of NaOMe and an excess of MeOH in THF provided the best conversion values towards the borylated product **2** (Table 2.1, entry 1). The optimal conditions for our system required 1.5 equivalents of the diboron reagent and total conversion of the substrate was achieved within 6 hours at room temperature. Also it is important to remark that the addition of catalytic amounts of basic phosphines such as PCy_3 contributed significantly to the improvement of the conversion (from 55 to 99%). The essential role of the phosphine in the activation of this kind of systems has already been studied.[17]

Table 2.1. Screening of bases for the borylative ring opening of **1**.

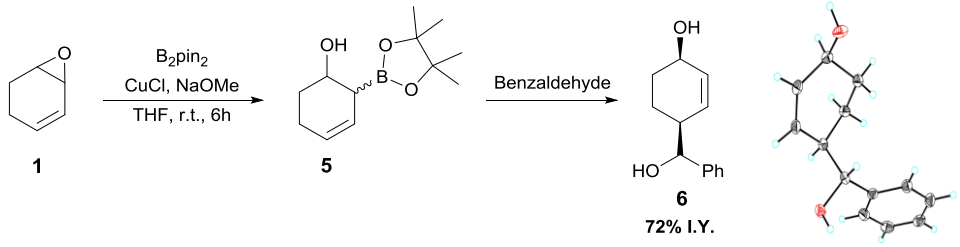
Entry	Base (mol%)	T (ºC)	Time (h)	Conv. (%)	I. Y. (%)
1	NaOMe (20)	25	6	99	62
2	NaOMe (10)	25	6	72	-
3	NaO^{t}Bu (10)	25	6	71	-
4	Cs_2CO_3 (10)	25	6	20	-

The organoborane **2** could be isolated and fully characterized for the very first time in a 62% I.Y. (Table 2.1, entry 1). One single diastereomer was formed in the reaction which was identified as the *trans* isomer by the subsequent derivatization in two ways: (i) oxidizing the C-B bond with $NaBO_3$ (Scheme 2.10 a) and (ii) reacting the organoboron with benzaldehyde following the previously reported protocols (Scheme 2.10 b).[11] The stereostructures of the corresponding 1,4-diol (**3**) and 1,3-diol (**4**) were determined by ^{1}H NMR spectroscopy.



Scheme 2.10. Metal-free borylative ring opening reaction of 3,4-epoxy-1-cyclohexene (**1**) and further derivatization reactions towards the diols **3** and **4**.

In addition, we carried out a comparative study using CuCl to activate the B_2pin_2 and we found out that the transition metal catalyzed reaction afforded the 2-pinacolboryl-3-cyclohexen-1-ol (**5**) via S_N2 addition. Thus, the presence of Cu(I) catalyst and a base favored the formation of Cu-Bpin species,[1,9] and the nucleophilic Bpin moiety attacked the oxirane group, while the C=C double bond remained intact. In this particular case, the product **5** could not be isolated but its reaction with benzaldehyde provided the expected 4-hydroxy-cyclohex-2-enyl-phenyl-methanol (**6**) species (Scheme 2.11). The X-Ray structure of **6** confirmed the *cis* arrangement of the 1,4-substituents on the disubstituted cyclohexene (Scheme 2.11). This results are clearly different to the ones reported by Tortosa[12] that have been explained above, where the obtained product is the *anti* 1,4-product. This different behavior of the copper salt must be due to the absence of phosphine in our case, which would make the copper more likely to directly attack the oxirane ring.

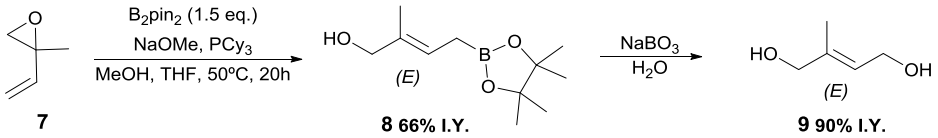


Scheme 2.11. Copper (I) mediated chemoselective borylation of the epoxide functional group of 3,4-epoxy-1-cyclohexene (**1**). X-Ray structure of 4-hydroxy-cyclohex-2-enyl-phenyl-methanol (**6**) species.

To survey the scope of the organocatalytic borylative ring-opening methodology, we next studied the reaction between the adduct $[B_2pin_2{\cdot}OMe]^-$ and 2-methyl-2-vinyloxirane (**7**). We found out that, as in the case of the cyclic

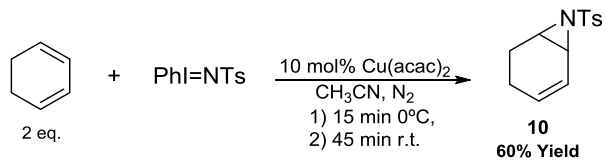
epoxide **1**, the C-B bond was formed *via* a bimolecular allylic substitution. This reaction was carried out at 50 ºC and left overnight to achieve complete conversion.

The relative position of the functional groups was determined by the oxidation of the allylboronate **8** with $NaBO_3$ to afford the corresponding diol 2-methyl-1,4-but-2-endiol (**9**) (Scheme 2.12). By comparison with previously reported ^{1}H NMR data for the *E* isomer of **9**,[18] we determined that **8**, was formed exclusively as the *E* isomer.



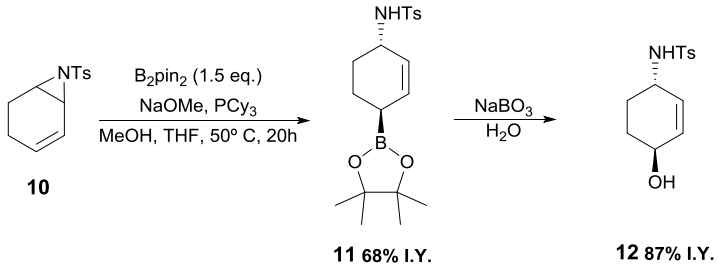
Scheme 2.12. Borylative ring opening of the vinyl epoxide **7** and subsequent oxidation of the allylboronate **8** with $NaBO_3$.

Next we focused our efforts on the synthesis of vinyl aziridines to be subsequently tested under our borylative ring opening methodology. We synthesized the vinyl aziridine 3,4-aziridine-1-cyclohexene (**10**) by the Evans-type direct monoaziridination of cyclohexadiene with the Yamada reagent [*N*-(*p*-toluenesulfonyl) imino]iodinane (PhI=NTs) (Scheme 2.13).[19]



Scheme 2.13. Aziridination of 1,3-cyclohexadiene with PhI=NTs reagent.

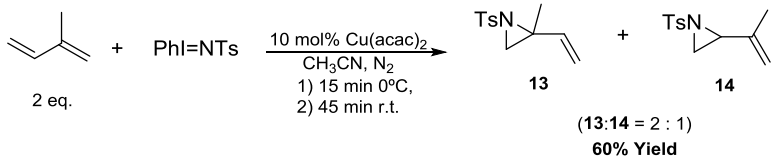
Next we tried the borylative ring opening reaction of the vinyl aziridine **10** under the same initial conditions but very low conversion was observed at 6h. An increase of the temperature to 50 ºC and reaction time set to 20 h was crucial to obtain again the S_N2' product in 90% conversion. The 4-pinacolboryl-2-cyclohexen-1-tosylamine product **11** was isolated and characterized exclusively as the *anti* 1,4-product by comparison with the reported data (Scheme 2.14).[11]



Scheme 2.14. Metal-free borylative ring opening reaction of the aziridine **10**.

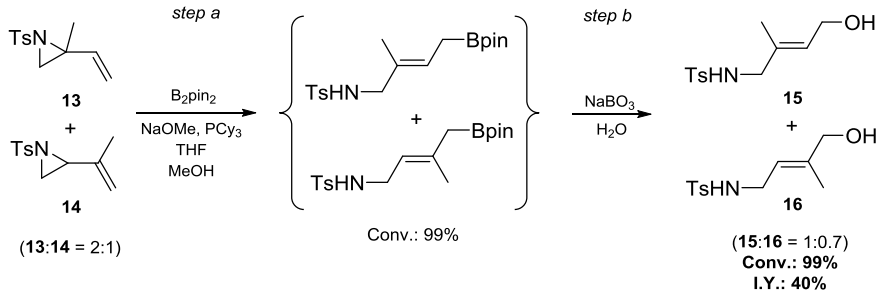
Subsequently, the organoborane **11** was oxidized following the oxidation protocol with $NaBO_3$ towards the 4-tosylamino-2-cyclohexen-1-ol **12** product, which could be isolated in a 87% yield.

The substrates 2-methyl-2-vinylaziridine (**13**) and 3-methyl-2-vinylaziridine (**14**), were prepared as a 2:1 mixture following the same previous aziridination procedure for the isoprene substrate (Scheme 2.15).[19c] Unfortunately we were unable to separate product **13** from **14** by the standard purification methods.



Scheme 2.15. Aziridination of isoprene with PhI=NTs reagent.

The borylative ring opening reaction of the mixture of **13** and **14** proceeded with total conversion towards a mixture of amino functionalized allyl boronate compounds, which could be isolated after oxidation as a mixture of 3-methyl-4-tosylamino-2-buten-1-ol (**15**) and 2-methyl-4-tosylamino-2-buten-1-ol (**16**) (1:0.7) (Scheme 2.16).[11]



Scheme 2.16. Borylative ring opening of **13** and **14**, followed by *in situ* oxidation.

The prevalence of the borylative ring-opening via S_N2' pathway has also been demonstrated in these acyclic vinyl aziridines. It has to be mentioned that byproduct formation was not observed and the isolated yields of the products were only moderate due to the instability of the functionalized allylic boronate compounds.

2.3.2 DFT studies

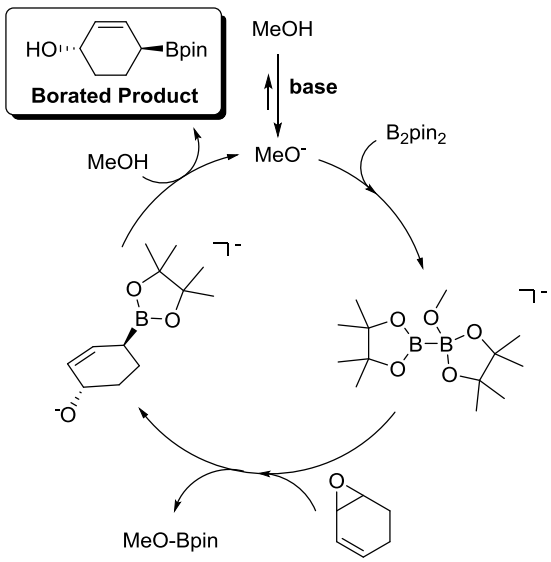
2.3.2.1 Computational details

All calculations were performed by utilizing Amsterdam Density Functional (ADF v2009.01) package.[20] Molecular structures for all species were optimized without constraints using a triple-ξ plus polarization Slater basis on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[21] For geometry optimizations we used the local VWN correlation potential[22] together with the Becke exchange and the Perdew correlation[23] (BP86) generalized gradient (GGA) corrections. Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequency calculations. Solvent effects were introduced by using the continuous solvent model COSMO.[24] Single-point energy evaluations at the metahybrid M06[25] level were performed self-consistently.

For the pKa calculation, molecular structures of the intermediates and protonated products were calculated without constraints using Gaussian 09, Revision A.02,[26] with the hybrid B3LYP[27] functional and 6-31+G*[28] as a basis set. Solvent effects (dimethylsulphoxide, DMSO) were introduced by using the Polarizable Continuum Model (PCM).[29]

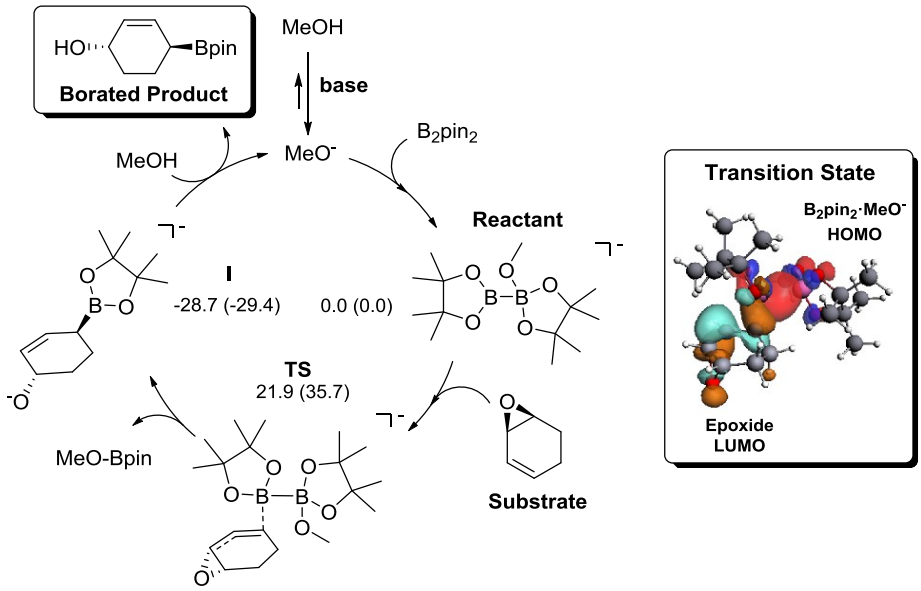
2.3.2.2 Mechanistic proposal

In order to get deeper insights into the mechanism of the organocatalytic borylative ring opening of vinyl epoxides and aziridines, we carried out a DFT based study on the main intermediates and transition states. As our group has previously shown,[14i, 14l, 14n] the crucial additives for activating B_2pin_2 are Brönsted base and MeOH to generate the $[B_2pin_2{\cdot}OMe]^-$ adduct. Also in the present case, this adduct is the key starting point in our proposed mechanism for the base/alcohol borylative ring-opening of epoxides and aziridines taking 3,4-epoxy-1-cyclohexene (**1**) as model substrate (Scheme 2.17). Next, this activated adduct attacks a molecule of substrate generating the borylated intermediate that finally gets protonated to yield the final product.



Scheme 2.17. Proposed reaction mechanism for the borylative ring opening.

We started optimizing the structure of the $[B_2pin_2{\cdot}OMe]^-$ adduct and we considered it as the origin of the energies. In the next step, we found a transition state (**TS**) described as a S_N2' reaction that involves the nucleophilic attack of the adduct sp^2 boron moiety at the C_1 carbon atom of the double bond. This interaction was identified as the overlap between the strongly polarized B–B σ bond (HOMO) of the activated diboron reagent and the anti-bonding π* orbital (LUMO) of the vinyl epoxide (Scheme 2.18).



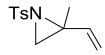
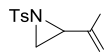
Scheme 2.18. Proposed reaction pathway for the borylative ring-opening of vinyl epoxides and vinyl aziridines with B_2pin_2. Electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level relative to $[B_2pin_2{\cdot}OMe]^-$ adduct plus 3,4-epoxy-1-cyclohexene (**1**) as a model substrate. All values are in kcal·mol^{-1}. Representation of the overlap of the HOMO and LUMO orbitals for the Transiton State (**TS**).

The structural features of the **TS** clearly reflect the cleavage of the B–B bond (from 1.701 in free B_2pin_2, to 1.755 in $[B_2pin_2{\cdot}OMe]^-$, to 2.096 in **TS** (Å)), and the formation of the new B–C_1 bond (1.988 Å). Also, according to the C–C bond distances, an allylic type rearrangement is taking place, the C_1–C_2 bond distance increases (from 1.344 in the substrate to 1.417 Å in **TS**) while the C_2–C_3 bond distance decreases (from 1.483 in the substrate to 1.438 Å in **TS**), suggesting the formation of the new C_2=C_3 double bond. Importantly, the C_3-C_4-O angle increases only slightly from the substrate to the transition state (from 60.6 to 67.9º). Although this fact is indicative of concomitant opening of the epoxide ring, regarding these parameters the transition state is rather early. Remarkably, the enhancement of electron density in the oxygen atom (Voronoi charge in the substrate -0.24 to -0.36 in the **TS**) corroborates that charge redistribution has already taken place. The **TS** structure releases the MeO-Bpin byproduct and directly leads to the formation of an anionic intermediate **I** in which the epoxide ring is completely open (The C_3-C_4-O angle is 110.6º and the Voronoi charge in the oxygen atom is -0.74). Further protonation of this **I** species in the presence of an excess of MeOH provides the de-

sired allyl boronate product **2**, and in this way methoxide ions are regenerated.

The configuration of the final allylboronate product was exclusively characterized as the *trans* isomer since the nucleophilic attack of the sp^2 boron moiety to C_1 occurs in *anti* with regard to the epoxide functional group. However we also evaluated the attack in *syn* that would lead to the *cis* isomer. In this line, the **TS-*syn*** was found to be more energetically demanding ($\Delta\Delta E^{\neq}$= +5.8; $\Delta\Delta G^{\neq}$= +4.3 kcal·mol^{-1}) than **TS**. These computational findings are in good agreement with the experimental data, since with all the studied substrates, the *trans* allylboronate product was the only one observed. Note that both transition states **TS** and **TS-*syn*** were located and characterized for the other substrates (1, 7, 10, 13 and 14), being the *syn* attack the more energetically demanding in all the cases (Table 2.2).

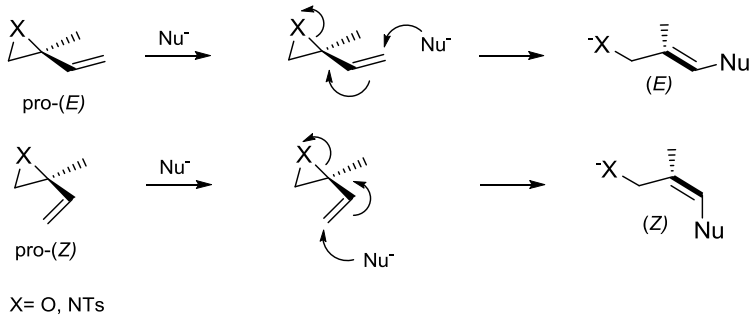
Table 2.2. Relative Gibbs energy (kcal·mol^{-1}) for the *anti* and *syn* **TS** and **I** species of the studied vinyl epoxides and aziridines.[a]

Entry	Substrate	*Anti*		*Syn*	
		$\Delta G^{\neq}$	ΔG_r	$\Delta G^{\neq}$	ΔG_r
1	**1** 	35.7 (34.2)	-29.4 (-31.4)	40.0 (40.1)	-28.9 (-31.8)
2	**7** 	31.0 (29.8)	-31.5 (-31.9)	30.7 (35.5)	-31.5 (-31.9)
3	**10** 	26.7 (27.1)	-54.4 (-58.9)	33.0 (34.6)	-47.6 (-52.2)
4	**13** 	25.3 (27.1)	-56.2 (-56.4)	26.2 (32.3)	-62.7 (-62.8)
5	**14** 	27.0 (31.0)	-61.7 (-62.0)	28.0 (33.2)	-52.0 (-52.7)

[a] Molecular geometries for all the species were optimized using BP86 as a functional. Single point energies at the metahybrid M06 level are in parenthesis.

At this point, we observed no significant differences in energies between the functionals BP86 and M06, since only single points were performed. Higher energy differences might be obtained if all the structures were optimized for both functionals.

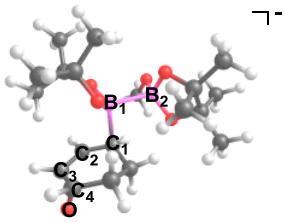
Note also that for the acyclic substrates, rather than the *anti* or *syn* attack, the important point to consider is the disposition of the double bond respect the oxirane group. Thus, we can find pro-(*E*) and pro-(*Z*) configurations of the substrate (Scheme 2.19). For the acyclic epoxide the pro-(*E*) appeared to be ~1 kcal·mol^{-1} more stable and its corresponding **TS** was less energetically demanding ($\Delta\Delta E^{\neq}$= -0.6; $\Delta\Delta G^{\neq}$= -1.2 kcal·mol^{-1}). These values are in agreement with the sole observation of the *E* isomer.



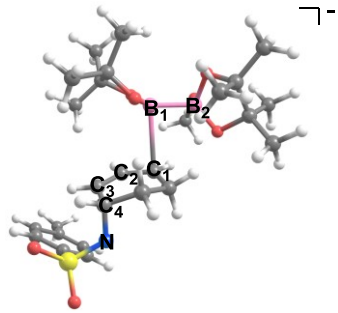
Scheme 2.19. Configurations of the acyclic substrates.

Although the *anti* nucleophilic attack is energetically favored for all the considered substrates, we did find notable structural differences between the **TS** for vinyl epoxides and the analogous tosyl aziridines. Considering the bond distances of the new C_2-C_3 bonds as well as the bond angles C_3-C_4-O/N in the **TS**, it is clear that the structures of the **TS** for the epoxides (Table 2.3, entries 1 and 2) resemble more the features of reactants in free form than the intermediate **I**. Contrarily, the structural features of **TS** for aziridines are closer to those of the intermediates **I**; that is, the C_2-C_3 bond distances are shorter than those for epoxides and the C_3-C_4-N bond angles are larger (Table 2.3, entries 3, 4 and 5). Epoxides have an early **TS** while tosyl aziridines have a late **TS**. This can be understood taking into account that the developed charge on the nitrogen due to the charge redistribution upon the nucleophilic attack is stabilized by the tosyl group.

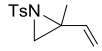
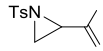
Table 2.3. Molecular structures for the model **TS** with the vinyl epoxides and aziridines. Selected bond distances (d) are given in Å and bond angle (α) in º.



TS-like-reactants



TS-like-product

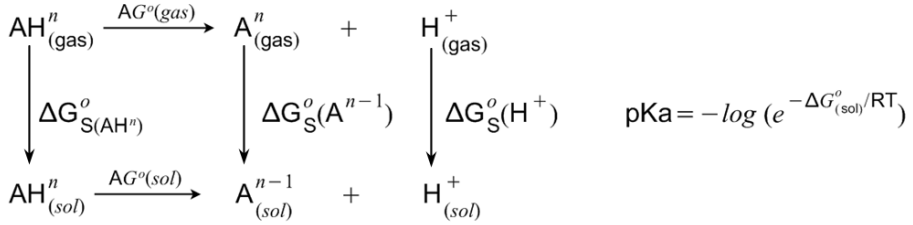
Entry	Substrate	d(C_2-C_3)	d(C_3-O)	α (C_3-C_4-O/N) TS	α (C_3-C_4-O/N) I
1	**1** 	1.438	1.624	67.9	110.6
2	**7** 	1.418	1.865	80.9	112.1
3	**10** 	1.399	2.118	91.1	113.7
4	**13** 	1.410	2.207	96.0	112.1
5	**14** 	1.410	2.102	90.5	110.4

This stabilizing effect of the tosyl group is also reflected in the energy values of the **TS**; there is a clear trend: the **TS** for the studied aziridines are less energetically demanding than for epoxides (Table 2.3, entries A, B, C, D and E. Note that both $\Delta E^{\neq}$ and $\Delta G^{\neq}$ values for aziridines are approx. 9-10 kcal·mol^{-1} lower than those for epoxides). Thus, tosyl aziridines seem to be more reactive than epoxides to undergo the S_N2' borylative ring-opening process. Also, the resulting anionic **I** species with tosyl aziridines are thermodynamically more stable than the corresponding epoxides derived (Table 2.3, entries A, B, C, D and E, ΔE_r and ΔG_r values, difference of approx. 30 kcal·mol^{-1}). Remarkably, independently of the DFT functional used or considering dispersion effects with the M06 functional, or even including solvent effects, the general trend remains equal: vinyl tosylaziridines are more reactive, and their products are more stable, than the corresponding epoxides. Comparing the studied vinyl

epoxides, the energy barrier for the **TS** of the acyclic vinyloxirane **7** is lower than that for the cyclic **1** (Table 2.3, entry A with respect to B, $\Delta\Delta E^{\neq}$= -4.1; $\Delta\Delta G^{\neq}$= -4.7 kcal·mol^{-1} lower). Aziridines follow the same trend (Table 2.3, entry C with respect to D, $\Delta\Delta E^{\neq}$= -2.3; $\Delta\Delta G^{\neq}$= -1.4 kcal·mol^{-1} lower), being less energetically demanding than epoxides. This result can be rationalized by the fact that terminal double bonds are more reactive than internal ones. Note the high stability of the aziridine derived intermediates in which the negative charge is stabilized by the tosyl group.

The cycle starts with the deprotonation of a molecule of MeOH by the base. However, in our postulated cycle, the anionic intermediate species **I** is the responsible of the next deprotonation of the molecule that generates the MeO$^-$ species to close the catalytic cycle.

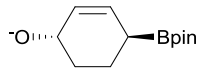
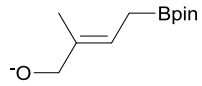
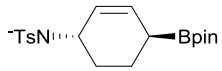
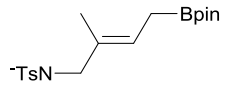
Thus, we computed the pKa for the intermediates based on the Born-Haber cycle using the known solvation energy of the proton ($\Delta G^{o}_{S}(H^+)$= -265.9 Kcal·mol^{-1}) (Scheme 2.20).[30]



Scheme 2.20. Born-Haber cycle.

As expected, vinyl-alkoxides are more basic than the corresponding vinyl-amidures (Table 2.4). At the same level of theory, we evaluated the pKa of the strong Verkade's base (23.4), a value that almost matched the experimental value (26.8).[17] The obtained values suggest that both vinyl-amidures and vinyl-alkoxides are as basic as, or even more basic than, Verkade's super base, so they are able to deprotonate methanol.

Table 2.4. Computed pKa values for the intermediate species.

Entry	I	pKa
1		35.6
2		34.5
3		22.3
4		23.6

2.4 Conclusions

We have developed a methodology for the metal-free borylative ring opening of vinyl epoxides and vinyl aziridines. The sole addition of B_2pin_2 with a base and MeOH provided *in situ* the $[MeO{\cdot}B_2pin_2]^-$ adduct formation. As a consequence of this Lewis acid-base interaction, the sp^2 Bpin moiety acquired an enhanced nucleophilic character that allowed the attack at the conjugated C=C of epoxides or aziridines, throughout a S_N2' pathway. The reaction took place exclusively on the contrary face of the oxirane or aziridine ring, giving rise to the *anti* borylated products. Further derivatization of the allylboronate products via oxidation or reactivity with benzaldehyde allowed us to confirm the stereostructures.

From a theoretical point of view, we proposed a plausible mechanism for the metal-free borylation of cyclic and non-cyclic vinyl epoxides and aziridines. The mechanism is in accordance with our experimental results and helps to understand the role of each reagent in the reaction.

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UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

"Look up at the stars and not down at your feet.
Try to make sense of what you see,
and wonder about what makes the universe exist.
Be curious."

Stephen Hawking

3. Novel synthesis of *β*-seleno and *β*-sulfido carbonyl compounds

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UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
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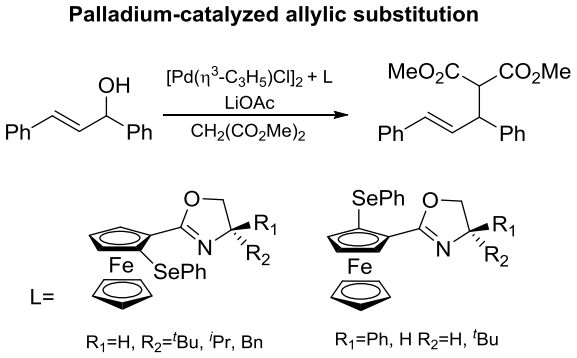
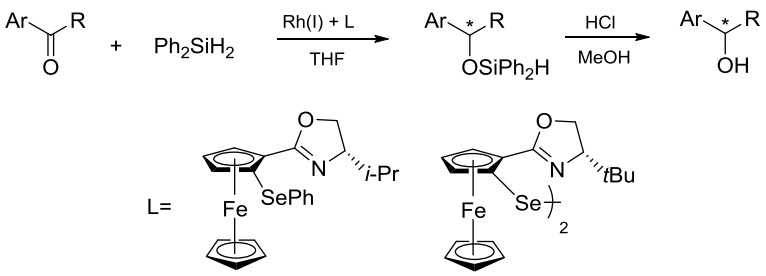
3.1 Introduction

There has been recent increasing interest in the generation of organoselenium compounds for their extensive applications in organic synthesis, material science and ligands for transition metal complexes to be used in catalysis (Scheme 3.1).[1]





Scheme 3.1. Examples of selenium-containing ligands and their application in metal-catalyzed reactions.

Because of their antioxidant character, organoselenides have been widely studied and tested in biological processes such as inhibitors,[2] enzymes[3] and even as therapeutic agents (Figure 3.1).[4] Among many other reactions, they have also been used as catalysts for oxidative halogenations due to the ability of selenium to undergo reversible oxidation-reduction processes.[5]

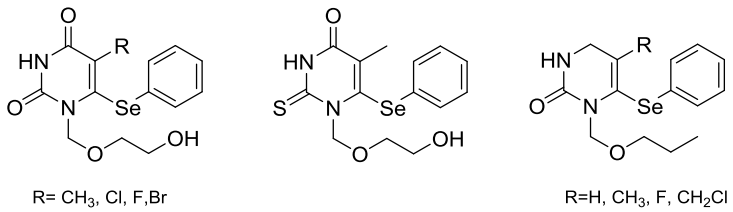


Figure 3.1. Some tested anti-HIV agents.

On the other hand, many organosulfides are products of great value[6] as well as natural products such as the pheromone grandisol.[7] They are also employed in the synthesis of relevant compounds such as the antibiotic penicillin[8] (Figure 3.2). It is also known that they are present in our food, playing a role in our immunomodulation[9] and disease prevention (Figure 3.2).[10] In addition, they find application in many other fields such as polymer science[11] or wastewater treatment[12] among other.

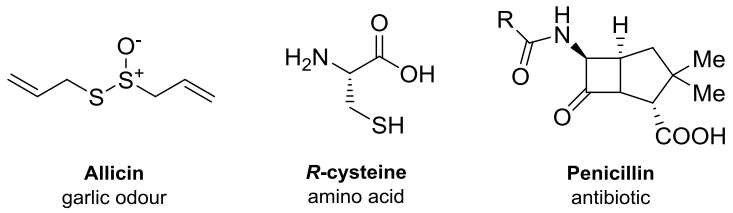


Figure 3.2. Bioactive organosulfide compounds.

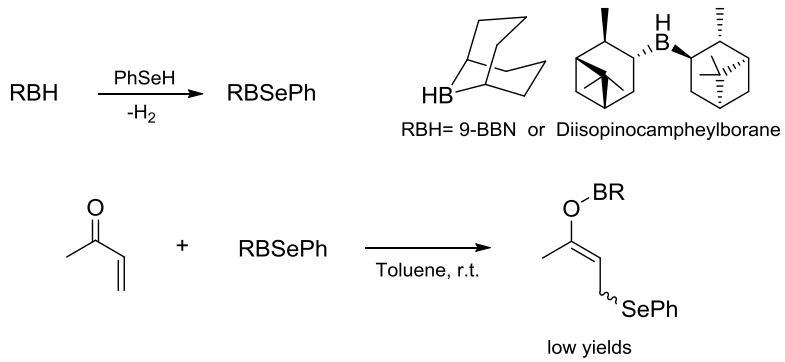
Due to their importance, both organoselenides and organosulfides have been targets of organic synthesis during the past century.

3.1.1 Synthesis of organoselenides and organosulfides

Of particular significance is the synthesis of selenium substituted carbonyl compounds which are well known to act as enone β-anion synthons.[13] Routes to these remarkable compounds either suffer from low yields and/or harsh reaction conditions utilizing the sensitive and malodorous selenols.

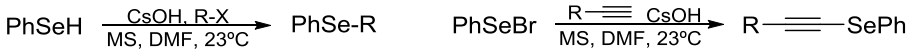
In 1980 Yano and co-workers reported a ruthenium catalyzed transformation of primary, secondary and tertiary amines to phenyl selenides in excellent yields.[14]

A later study by Leonard and Livinghouse showed that novel monomeric selenium boron compounds, derived from dialkylboranes, could be used as a gentle and efficient alternative to the starting selenols.[13c] Unfortunately, reactions with bulky *α,β*-unsaturated carbonyl compounds gave the corresponding organoselenium products in low yields, presumably due to the steric congestion arising from the bulky borane group (Scheme 3.2).



Scheme 3.2. Preparation of the first selenium boron compounds and further reactivity with *α,β*-unsaturated carbonyl compounds.

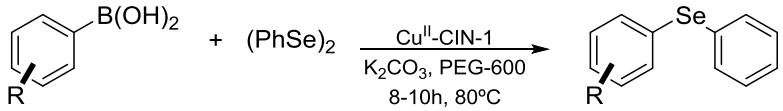
In 2004, Salvatore and co-workers developed a new one-pot method for the preparation of unsymmetrical selenides. In the presence of cesium hydroxide, molecular sieves, and DMF, benzeneselenol undergoes direct alkylation with various alkyl halides for the synthesis of alkyl phenyl selenides in moderate to excellent yields. Another method to prepare unsymmetrical organoselenides was also completed by coupling terminal alkynes with benzeneselenyl bromide. In addition, the synthesis of a selenopeptide was also accomplished using this methodology (Scheme 3.3).[15]



Scheme 3.3. Alkylation of benzeneselenol and benzeneselenyl bromide.

More recently, it was reported that the reagent PhSe-ZnCl can be conveniently used to effect Michael addition like reactions to vinyl ketones. The reactions take place at room temperature in THF or water.[16]

Last year Islam and co-workers reported a new heterogeneous copper catalyst synthesized by immobilizing Cu(II) onto the surface of a nitrogen rich porous covalent imine network material CIN-1. The material was successfully used to catalyze the cross-coupling reaction between aryl boronic acids and diphenyldiselenide to synthesize unsymmetrical organoselenides. In addition, the catalyst was recycled for six repetitive runs without any appreciable loss of catalytic activity suggesting its potential usefulness in C–Se bond forming reaction (Scheme 3.4).[17]

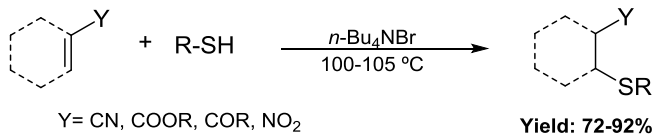


Scheme 3.4. Cu^{II}-CIN-1 catalyzed phenyl selenation of aryl boronic acids.

Concerning β-sulfido carbonyl compounds, their synthesis has been principally achieved by the conjugate addition of thiols to α,β-unsaturated carbonyl compounds.[18] Despite the mild nucleophilicity of the sulfur moiety in thiol reagents,[19] the reaction conditions frequently lead to the formation of byproducts from side reactions such as self-condensation, polymerization or rearrangements.[20]

Metal catalysts such as ruthenium(III) chloride,[21] cerium(III) chloride,[22] or indium(III) chloride[23] are required to activate both the substrate and the reagent and promote the formation of C_β-S bond in a precise way. Also asymmetric induction can be achieved.[24]

During the last years many organic species have been proved to work as organocatalysts in this sort of systems. Interestingly, these reactions can also be catalyzed using ionic liquids (Scheme 3.5)[25] and can remarkably be performed in water as well.[26]

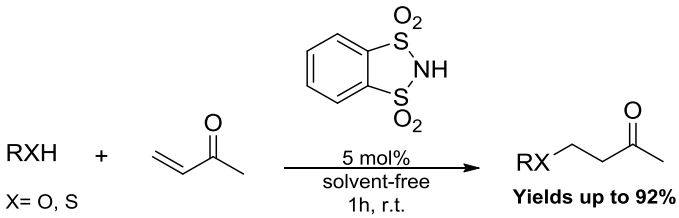


Scheme 3.5. Ionic liquid-catalyzed addition of thiols to electron deficient alkenes.

In 2004, Node and co-workers reported the development of new odorless thiols (dodecanethiol, 4-n-heptylphenylmethanethiol, 4-trimethylsilylphenyl-

methanethiol, 4-trimethylsilylbenzenethiol) and an odorless sulfide (1-methylsulfanyldodecane) and their applications in many reactions such as Michael addition.[27]

Recently, Dughera and co-workers reported the hetero-Michael reactions among various oxygen, sulfur, and nitrogen nucleophiles and *α,β*-unsaturated compounds in the presence of catalytic amounts of *o*-benzenedisulfonimide as Brønsted acid organocatalyst. Under solvent-free very mild reaction conditions, they achieved good product yields. After the reactions, the organocatalyst was easily recovered, purified, and reutilized (Scheme 3.6).[28]

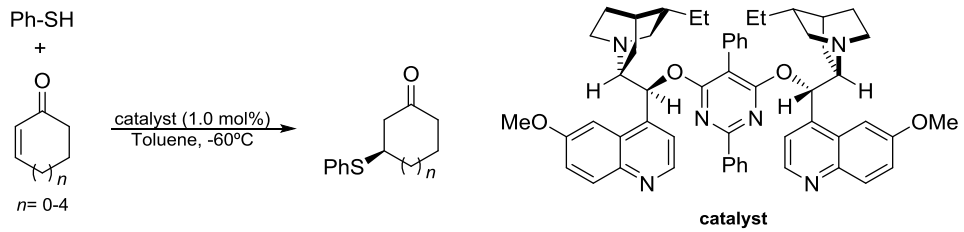


Scheme 3.6. Organocatalytic oxa-Michael and thia-Michael reactions.

However, the first example of asymmetric organocatalytic addition of thiols to cyclic conjugated enones was reported back in 1981 by Wynberg and co-workers.[29] They utilized chiral *β*-hydroxy amines as catalysts and studied the mechanism of the reaction.

Next year Mukaiyama and co-workers explored the catalytic asymmetric addition of thiols to 2-cycloalkenone by using the chiral amino alcohols, derived from L-hydroxyproline or (*S*)-proline, as base catalysts. Good optical yields (up to 88%) were achieved using this methodology.[30]

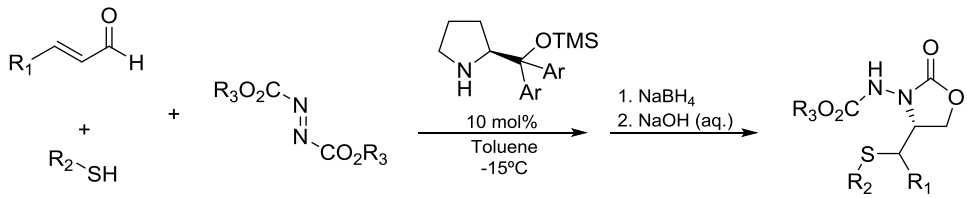
In 2003 Deng and co-workers reported a highly enantioselective 1,4-addition of thiols to cyclic enones catalyzed by a modified biscinchona alkaloid. Selectivity values ranging from 93 to >99 % *e.e.* were achieved for the addition of 2-thionaphthol to cyclic enones (Scheme 3.7).[31]



Scheme 3.7. Enantioselective 1,4-addition of thiols to cyclic enones.

Later on 2005, Cheng and co-workers utilized a bifunctional chiral organocatalyst comprising thiourea and tertiary amine groups that acted as efficient catalyst for asymmetric Michael addition of arylthiols to *a,β*-unsaturated carbonyl compounds with enantioselectivity values up to 85%. Also, asymmetric *a*-protonation reaction (up to 60% *e.e*.) was obtained in the presence of the bifunctional catalyst.[32]

At the same time, Jørgensen and co-workers reported an organocatalytic asymmetric multicomponent domino and a conjugated addition reaction to *a,β*-unsaturated aldehydes. The multicomponent reactions proceed to give enantiopure aminothiols in moderate to good yields (38–72%) and with excellent *e.e.* values. Furthermore, organocatalyzed thiol additions to *a,β*-unsaturated aldehydes were shown to take place in good yields (up to 87%) and enantioselectivity values up to 97% *e.e.* (Scheme 3.8).[33]

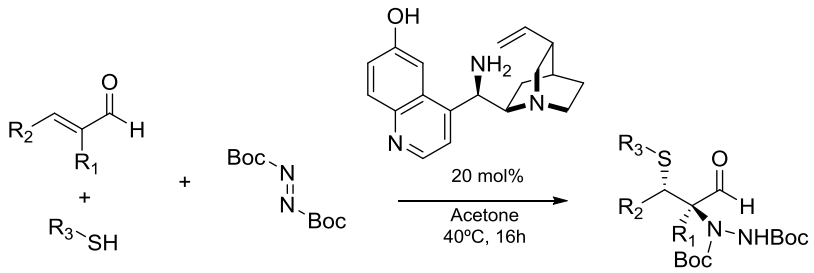


Scheme 3.8. Asymmetric organocatalytic domino reactions.

In 2008 Melchiorre and co-workers reported a highly enantioselective organocatalytic sulfa-Michael addition of benzyl and *tert*-butyl mercaptans to *a,β*-unsaturated ketones.[34] The catalytic use of a primary amine salt in which both the cation and the anion are chiral was crucial in the obtaining of a large variety of optically active products in high yields and excellent stereocontrol (up to 96 % *e.e.*).

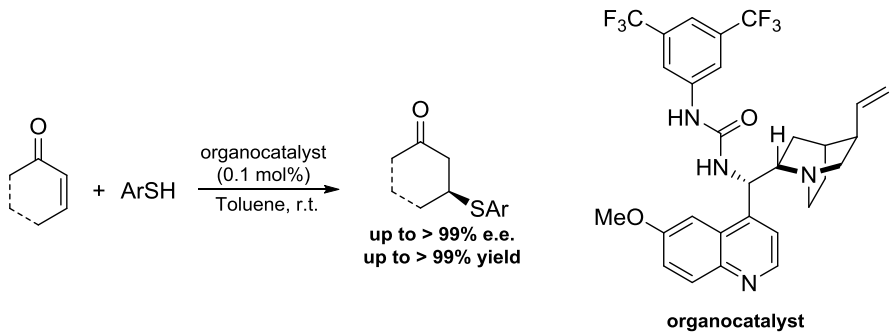
The next year, they also reported organocatalytic cascade reactions with *a,β*-unsaturated aldehydes.[35] In this case, they used a quinuclidine derivative

with a pendant primary amine as organocatalyst to achieve a sulfa-Michael/amination strategy (Scheme 3.9).



Scheme 3.9. Organocatalytic sulfa-Michael/amination cascade reactions to *α,β*-unsaturated aldehydes.

In 2010 Singh and co-workers shown a cinchona alkaloid-derived urea as an efficient organocatalyst for enantioselective conjugate addition between thiols and various *α,β*-unsaturated ketones to provide optically active sulfides with high chemical yields and enantiomeric excess (Scheme 3.10).[36]



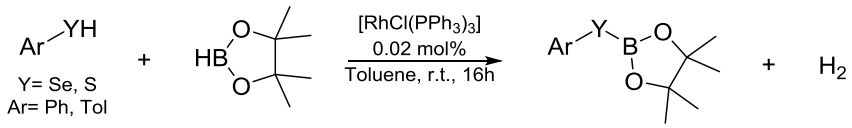
Scheme 3.10. Organocatalytic enantioselective synthesis of *β*-sulfido carbonyl compounds.

Later on 2011 Melchiorre and co-workers reported an asymmetric sulfa-Michael addition to *α*-branched enones catalyzed by the same quinuclidine derivative used on their previous work.[35] Quantitative conversions and excellent enantiomeric excess values were achieved with this methodology towards both the *syn* or *anti* isomers in a selective way.[37]

3.1.2 The novel B-Se and B-S species. Synthesis and properties

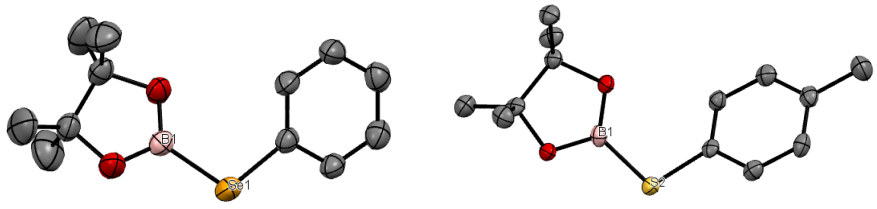
In this line, in 2006 Westcott's group developed and patented a family of novel B-Y species (Y= Se, S) but its reactivity was not further explored.[38] Later on 2013, Nolan's group added some examples to this

family of compounds.[39] These species were prepared under inert atmosphere by the metal catalyzed dehydrogenative borylation of the the corresponding selenol or thiol and one equivalent of the borane HBpin.[38-39] Complete conversion of the starting materials was achieved selectively using 0.02 mol% of Wilkinson's catalyst, $[RhCl(PPh_3)_3]$ at room temperature for 16 hours (Scheme 3.11).



Scheme 3.11. Synthesis of the B-Y (Y= Se, S) reagents by rhodium-catalyzed dehydrogenative borylation.

The PhSe-Bpin, TolS-Bpin, PhS-Bpin and BnS-Bpin species were successfully prepared and characterized using a number of physical methods including multinuclear NMR spectroscopy. In all cases, a peak in the ^{11}B NMR spectra around 30 ppm was observed, corresponding to the tricoordinated Bpin.[38-40] The species PhSe-Bpin and TolS-Bpin were also characterized by a single crystal X-ray diffraction study (Figure 3.3).[38]



PhSe-Bpin TolS-Bpin

Figure 3.3. Ball and stick diagram of X-ray of PhSe-Bpin and TolS-Bpin with hydrogen atoms omitted for clarity. Selected bond distances (Å): Se(1)-B(1) 1.950 and S(2)-B(1) 1.823.

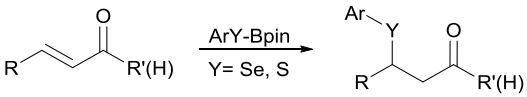
Interestingly, for these reagents the B-Y bond distance appears to be quite long compared to the B-B distance in B_2pin_2 (1.678 Å).[41] In addition, these compounds appeared to be very sensitive to the air and moisture. They decomposed rapidly to disulphides and diselenides plus multiple boron containing by-products if exposed to open air. This fact reflects that the reagent is very active, also in accordance with the elongated B-Y distance.

3.2 Motivation

Since the family of B-Se and B-S reagents had not been utilized in any kind of reaction, we started a collaboration project with Westcott's group to explore their reactivity.

Also, bearing in mind that most of the previously reported synthesis of organo-selenides and -sulfides require the presence of a metal catalyst to work; and based on the expertise of our group in the metal-free boron activation, we wanted to study the reactivity of these novel B-Se and B-S containing species with vinyl carbonyl compounds.

The activation of the Se-B and S-B bonds of these reagents in the presence of substrates was expected to lead to seleno- and sulfido- products without the need of expensive metal species (Scheme 3.12).

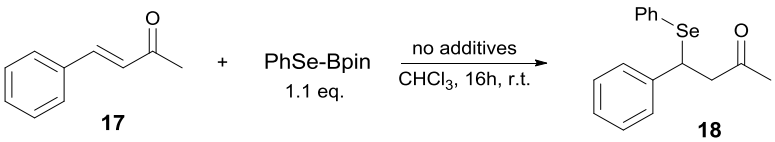


Scheme 3.12. Expected reactivity of the vinyl carbonyl compounds with B-S and B-Se reagents.

3.3 Results and discussion

3.3.1 Experimental results

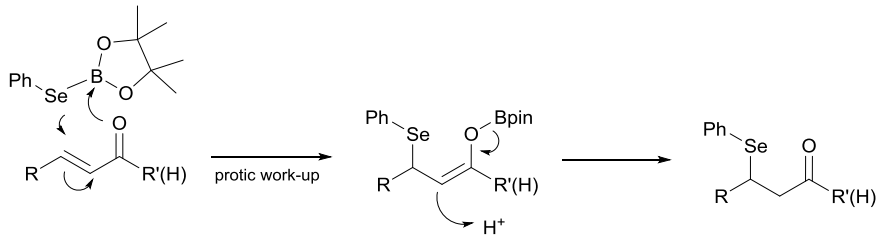
Our first experiments revealed that only by mixing the species PhSe-Bpin (1.1 eq) with 4-phenyl-3-buten-2-one (**17**) in chloroform, 27% conversion towards the β-selenated product **18** was achieved (Table 3.1, entry 1). Surprisingly, and in contrast to our group's previous metal-free β-boration works,[40b, 42] the reaction proceeded without the need of any base, additive or co-solvent presumably due to the high activity of the reagent (Scheme 3.13).



Scheme 3.13. First example of metal-free β-selenation of the substrate **17**.

This can be rationalized as a simple face-to-face activation of the B-Se species by the oxygen of the substrate itself. Thus, the carbonylic oxygen seems to

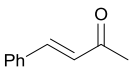
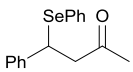
quaternize the B atom. Subsequent allylic rearrangement takes place to finally undergo protonolysis to yield the *β*-selenated product (Scheme 3.14).



Scheme 3.14. Reaction of the novel PhSe-Bpin species with α,β-unsaturated carbonyl compounds.

To optimize the reaction conditions we also tried benzene and THF as solvents. Both solvents gave similar vales of conversion but THF gave the best result (Table 3.1, entries 2 and 3). The addition of a higher excess of the reagent PhSe-Bpin to 1.5 eq. or the increment of the temperature to 60 ºC did not improve the conversion values either (Table 3.1, entries 4 and 5).

Table 3.1. Conjugate addition of PhSe moiety to α,β-unsaturated ketones.[a]

Entry	Substrate	Product	Solvent	Conv. (%)[b]	I.Y. [%]
1	 **17**	 **18**	$CHCl_3$	27	
2	„	„	benzene	30	
3	„	„	THF	40	[35]
4[c]	„	„	THF	24	
5[d]	„	„	THF	29	

[a]Reaction conditions: substrate (0.10 mmol), PhSe-Bpin (1.1 eq), THF (2 mL), 25 ºC, 16h. [b]Conversion calculated by NMR spectroscopy from an average of two essays. [c]PhSe-Bpin (1.5 eq), [d]T=60ºC.

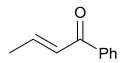
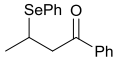
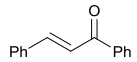
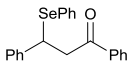
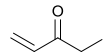
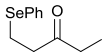
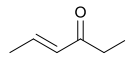
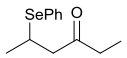
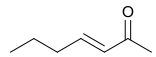
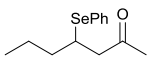
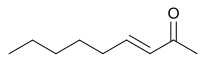
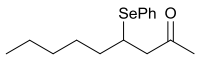
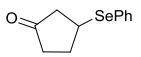
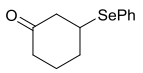
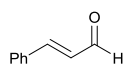
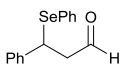
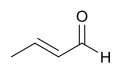
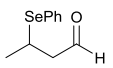
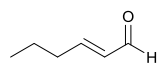
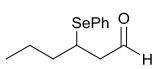
The scope of *α,β*-unsaturated ketones was next examined considering the best reaction conditions: THF as solvent, 1.1 equivalents of the PhSe-Bpin reagent for 16h at room temperature. After the reaction took place, in all cases it could be observed and isolated a PhSe-SePh fraction, as it was formed as a degradation byproduct.

The substrate *trans*-1-phenyl-2-buten-1-one (**19**) was more efficiently converted into the corresponding product **20** (Table 3.2, entry 1) than the analogue 4-phenyl-3-buten-2-one (**17**) (Table 3.1, entry 3) under the same reaction conditions. The conjugated Ph substituent to the C=O of the ketone seems to favor the interaction of the lone pair from C=O to Bpin. This hypothesis was also proved in the conjugate addition of PhSe moiety to *trans*-chalcone (**21**) achieving 67% conversion of the product **22** (Table 3.2, entry 2).

More remarkably, the aliphatic ketones 1-penten-2-one (**23**) and 4-hexen-3-one (**25**), which contain an ethyl group bonded to the carbonyl group, were quantitatively transformed into the corresponding *β*-(phenylseleno) substituted ketones **24** and **26**, up to 99% conversion (Table 3.2, entries 3-4). For the bulkiest aliphatic ketones 3-hepten-2-one (**27**) and 3-nonen-2-one (**29**), the conversion diminished slightly probably as a consequence of the steric hindrance around the C_β (Table 3.2, entries 5-6). Interestingly, the cyclic *α,β*-unsaturated ketones 2-cyclopenten-1-one (**31**) and 2-cyclohexen-1-one (**33**) were efficiently transformed into the *β*-seleno adducts **32** and **34** respectively (Table 3.2, entries 7-8). It is important because for these cases where the C=O and C=C are in *trans* each other, the lone pair from the oxygen seems to activate the Bpin as well.

Next, we turned our attention to explore the β-selenation of *α,β*-unsaturated aldehydes. In the case of cinnamaldehyde (**35**), the conjugate addition of PhSe was similar to the same reaction on 4-phenyl-3-buten-2-one (**17**), indicating that the functional groups ketone or aldehyde do not provide a significant difference on the C=O interaction with Bpin (Table 3.1, entry 3 and Table 3.2 entry 9). When the substrate was the aliphatic aldehyde crotonaldehyde (**37**), quantitative transformation into the desired product **38** was observed (99%, Table 3.2, entry 10), however steric factors on the *β*-carbon diminished the conjugate addition of PhSe on *trans*-2-hexenal (**39**) (Table 3.2, entry 11). Unfortunately, when *α,β*-unsaturated esters were subjected to the same reactivity, the corresponding *β*-(phenylseleno) substituted ester was not formed.

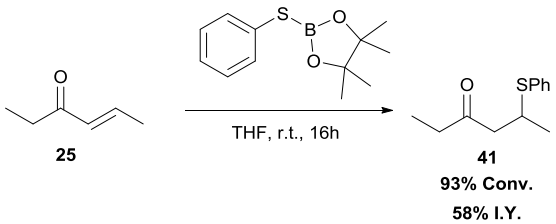
Table 3.2. Scope of vinylic ketones and aldehydes.[a]

Entry	Substrate	Product	Conv. (%)[b]	I.Y. [%]
1	 **19**	 **20**	69	[49]
2	 **21**	 **22**	67	[60]
3	 **23**	 **24**	99	[54]
4	 **25**	 **26**	94	[37]
5	 **27**	 **28**	78	[70]
6	 **29**	 **30**	65	[31]
7	 **31**	 **32**	65	[44]
8	 **33**	 **34**	93	[65]
9	 **35**	 **36**	41	[39]
10	 **37**	 **38**	99	[68]
11	 **39**	 **40**	53	[50]

[a]Reaction conditions: substrate (0.10 mmol), PhSeBpin (1.1 eq), THF (2 mL), 25 ºC, 16h. [b]Conversion calculated by NMR spectroscopy from an average of two essays.

After accomplishing a broad scope of *β*-(phenylseleno) ketones and aldehydes we predicted the same reactivity with the sulfur analogous PhS-Bpin. Therefore, we decided to test a reaction under the same conditions utilizing the substrate 4-hexen-3-one (**25**), which gave good conversion values for the selenium reagent. Indeed, these predictions were confirmed when the reagent PhS-Bpin was successfully added to the sub-

strate **25** to form the corresponding 5-phenylsulphanyl-hexan-3-one (**41**) (Scheme 3.15). The simplicity of the chemical operation, confirmed our prediction, but also opened a useful methodology to generate organosulfur compounds in a facile and highly efficient way, which contrast with all the previous reports involving 1,4-addition of thiols to vinylic carbonyl compounds, that require additional catalysts or bases.



Scheme 3.15. Extrapolated reactivity of PhS-Bpin species with the vinylic ketone **25**.

3.3.2 DFT study

3.3.2.1 Computational details

All calculations were performed by using the Gaussian 09 package[43] with the hybrid M06-2X functional.[44] The standard 6–311G** basis set was used to describe the H, C, B, O, N, Se and S atoms. Full geometry optimizations were performed without constrains. The nature of the stationary points encountered was characterized either as minima or transition states by means of harmonic vibrational frequencies analysis. The zero-point, thermal, and entropy corrections were evaluated to compute enthalpies and Gibbs free energies (T=298 K, p=1 bar). Hydrogen atoms have been omitted for clarity in the graphic representation of the geometries.

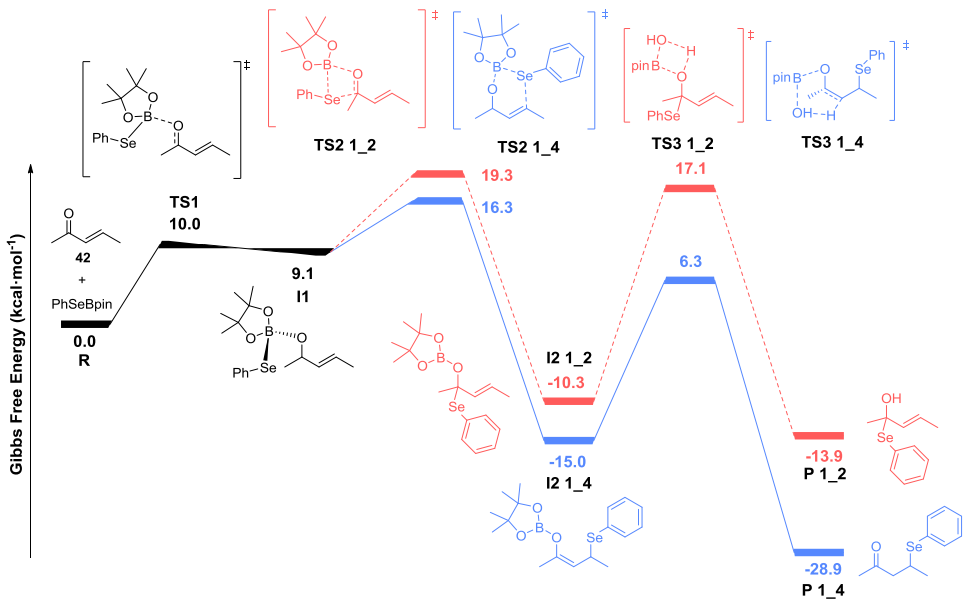
3.3.2.2 Mechanistic proposal

In order to establish a rational understanding of the reaction outcome we carried out theoretical studies by means of DFT methods to unravel the mechanism of this new reaction of PhSe-Bpin with vinyl carbonyl compounds.

We studied the reaction of the reagent PhSe-Bpin with a model substrate 3-penten-2-one (**42**). In the first step of our mechanistic proposal (Scheme 3.16), the carbonylic oxygen interacts with the empty *p* orbital of the boron atom, in the same way as other nucleophiles do (alkoxides,

carbenes), thus increasing the nucleophilic character of the PhSe moiety. Indeed, a first intermediate is formed (**I1**, bond distances Se-B=2.089, B-O=1.619, O-C_2=1.244 (Å)) which lies 9.1 kcal·mol^{-1} above the reactants. Note that in the electronic energy profile this intermediate is 5.8 kcal·mol^{-1} more stable than the two separated entities, and it is raised in free energy because the loss of translational entropy. All Gibbs free energy values provided herein do not include any additional entropy correction.

We located a transition state (**TS1**, bond distances Se-B= 2.039, B-O= 1.899, O-C_2= 1.234 (Å)) for the formation of intermediate **I1**, which reflects the activation of the Se-B bond as well (computed bond distance for the free reagent Se-B= 1.953 Å). The next step is the boron-selenium bond cleavage, which is concerted with the attack of the nucleophilic selenium to the electrophilic points of the substrate through a second transition state. Thus, selenium can attack either the *β* position (1,4-addition, **TS2 1_4**) or the carbonylic carbon (1,2-addition, **TS2 1_2**). In the **TS2 1_4** it can be observed that the Se-B distance increases (Se-B= 2.170 Å) while the B-O distance decreases (B-O= 1.551 Å). The electronic rearrangement of the double bond can be observed by the increase of the O-C_2 (O-C_2= 1.281 Å) and the decrease of the C_2-C_3 bond distances (ΔdC_2-C_3= -0.06 Å). In the **TS2 1_2** the increment of the Se-B bond distance (Se-B= 2.223 Å) can be observed as well as the B-O bond distance decrease (B-O= 1.539 Å) and the O-C_2 bond distance increase (O-C_2= 1.282 Å) (Scheme 3.16, Figure 3.4).



Scheme 3.16. Proposed reaction pathway for the reaction of PhSe-Bpin with 3-penten-2-one. The pathway for the direct addition is painted in red and for the conjugate addition is painted in blue. All Gibbs free energies are in kcal·mol^{-1}.

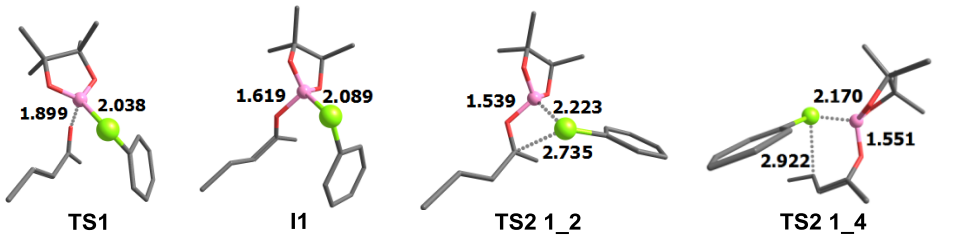


Figure 3.4. Optimized structures for the **TS1**, **I1**, **TS2 1_2** and **TS2 1_4** with the selected distances in Å.

It is important to highlight that all the activation energies for the 1,4-addition pathway ($\Delta G^{\neq}_{TS2\ 1\_4}$= 16.3, $\Delta G^{\neq}_{TS3\ 1\_4}$= 6.3 kcal·mol^{-1}) are less energetically demanding than the ones for the 1,2-addition ($\Delta G^{\neq}_{TS2\ 1_2}$= 19.3, $\Delta G^{\neq}_{TS3\ 1\_2}$= 17.1 kcal·mol^{-1}). Furthermore, the intermediate **I2 1_4** ($\Delta G_{I2\ 1_4}$= -15.0 kcal·mol^{-1}) and the product **P 1_4** ($\Delta G_{P2\ 1_4}$= -28.9 kcal·mol^{-1}) are more stable than their corresponding analogous **I2 1_2** ($\Delta G_{I2\ 1_2}$= -10.3 kcal·mol^{-1}) and **P 1_2** respectively (Scheme 3.16). In all the studied cases (Table 3.1) the corresponding seleno-alcohol **P 1_2** ($\Delta G_{P2\ 1_2}$= -13.9 kcal·mol^{-1}) was never experimen-

tally observed. Therefore, the 1,4-addition product **P 1_4** is obtained from both kinetic and thermodynamic reasons.

The HOMO orbital of **TS2 1_4** (Figure 3.5) reflects two interesting features: first, the big lobe located on the nucleophilic Se atom interacting with the *β*-carbon, and second, the building up of a Π orbital between the *α* and the carbonylic carbon atoms.

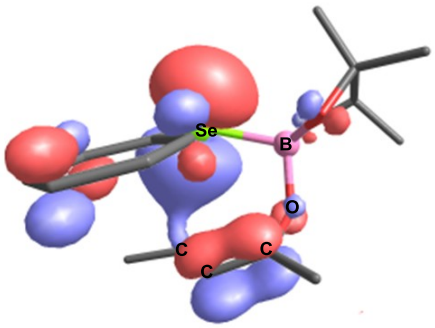


Figure 3.5. Graphic representation of the HOMO orbital for the **TS2 1_4** corresponding to the interaction of the selenium atom with the *β*-carbon.

3.3.2.3 Reagent comparison

At this point we decided to explore the reaction of the same substrate, 3-penten-2-one (**42**), with the sulfur (PhS-Bpin) and oxygen (PhO-Bpin) analogous of PhSe-Bpin theoretically. Thus, we computed the relative Gibbs free energies of the **TS1**, **I1**, **TS2 1_4** and **I2 1_4** structures for selenium, sulfur and oxygen borane reagents (Figure 3.6). The energies for PhSe-Bpin and PhS-Bpin resulted very similar, almost identical, and this indicated that both reactions might take place under the same conditions.

However, it is important to mention that in the case of the oxygen analogous the pathway is clearly different than the other two: no **TS1** was located, and the reaction would occur in only one step. Moreover, the activation energy in this case appeared to be much higher than for the Se and S reagents, and the reaction would lead to a product that is even less stable than the reactants (Figure 3.6).

Based on these theoretical arguments, one should expect the reaction to work for the PhS-Bpin reagent under the same reaction conditions than the

PhSe-Bpin reagent, but not to work for an oxygen equivalent based reagent. This outcome makes sense, since the formation of the stable byproduct RO-Bpin is always observed in the classical borylation reactions and it is usually the driving force of the reaction.

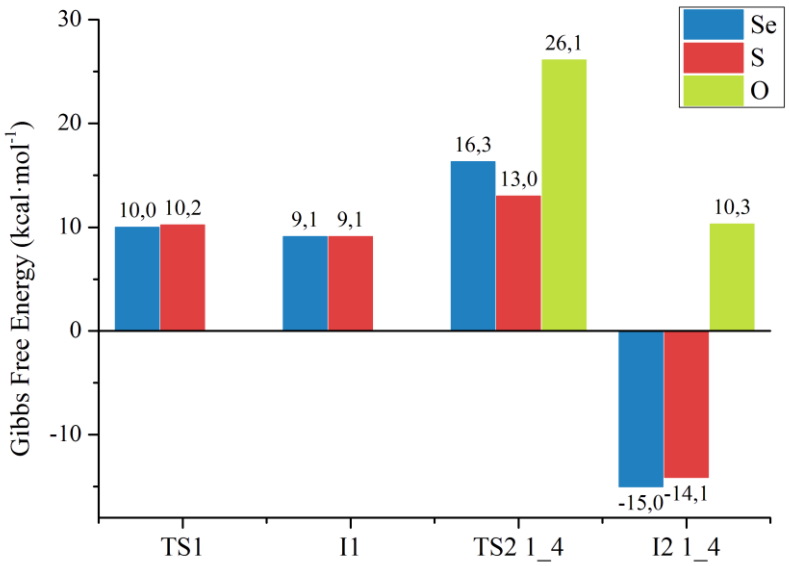


Figure 3.6. Relative Gibbs free energies of the most relevant species in the reaction of 3-penten-2-one with PhSe-Bpin (blue), PhS-Bpin (red) and PhO-Bpin (green).

In order to clarify the different nucleophilic character of the reagents PhSe-Bpin, PhS-Bpin, TolS-Bpin and PhO-Bpin we calculated the nucleophilicity index (N) based on relating the nucleophilicity with the computed highest occupied molecular orbital (HOMO) energy by the Kohn–Sham scheme[45] through the next formula introduced by Perez *et al*.[46]

$$N = E_{HOMO(Nu)}(eV) - E_{HOMO(TCE)}(eV),$$

where tetracyanoethylene (TCE) is taken as reference. In this scale, the nucleophilicity index for TCE is N= 0.0 eV, presenting the lowest HOMO energy in a long series of organic molecules already considered. According to a same author's latter study[16] the nucleophiles can be classified as strong, N > 3.00 eV, moderate, 2.00 eV < N < 3.00 eV, and marginal, N < 2.00 eV. Table 3 collects the N values for the PhSe-Bpin, TolS-Bpin (TolS=4-MeC_6H_4S), PhS-Bpin, PhO-Bpin and BnS-Bpin species. Hence, the first four species have a

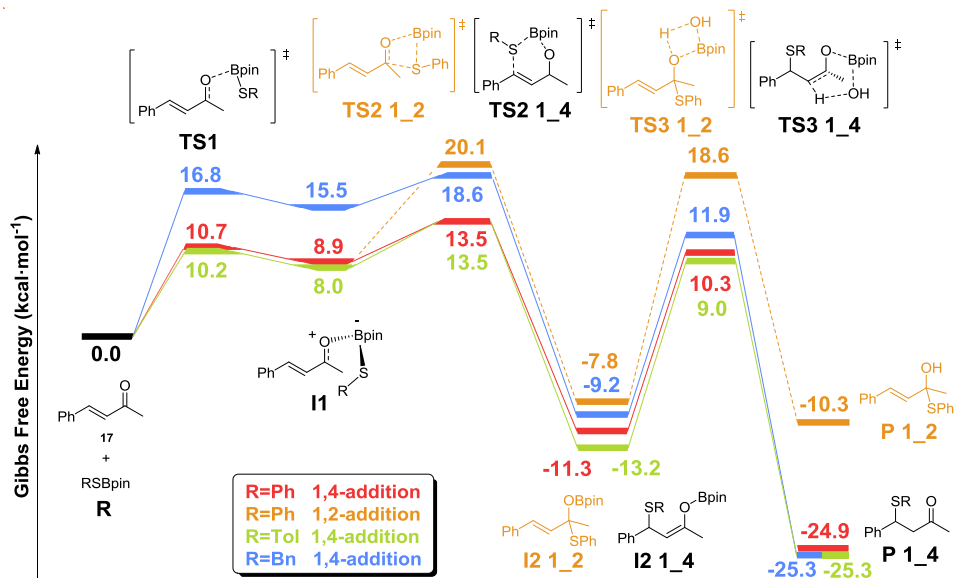
strong nucleophilic character whereas BnS-Bpin is considered as a moderate nucleophile. These results indicate that BnS-Bpin reagent should be less reactive than TolS-Bpin and PhS-Bpin. Also, they show the expected trend in nucleophilicity: Se > S > O.

Table 3.3. Calculated Nucleophilicity indexes (N) for PhSe-Bpin, TolS-Bpin, PhS-Bpin and BnS-Bpin reagents. All energies are in eV.

PhSe-Bpin	TolS-Bpin	PhS-Bpin	PhO-Bpin	BnS-Bpin
3.48	3.35	3.24	3.09	2.89

To complete the study, and in order to predict the reactivity of the other reagents, we computed the relative Gibbs free energies of the species involved in the thioboration of 4-phenyl-3-buten-2-one (**17**) through 1,2- and 1,4-addition with PhS-Bpin, as well as the 1,4-addition with TolS-Bpin and BnS-Bpin (Scheme 3.17). It can be observed that for the 1,2-addition of the PhS-Bpin reagent the activation free energies of both the **TS2 1_2** ($\Delta G^{\neq}_{TS2\ 1\_2}$= 20.1 kcal·mol^{-1}) and **TS3 1_2** ($\Delta G^{\neq}_{TS3\ 1_4}$= 18.6 kcal·mol^{-1}) are higher than the corresponding ones for the 1,4-addition pathway ($\Delta G^{\neq}_{TS2\ 1_4}$= 13.5 kcal·mol^{-1} and $\Delta G^{\neq}_{TS3\ 1\_4}$= 10.3 kcal·mol^{-1}, respectively). Also, the intermediate **I2 1_2** ($\Delta G_{I2\ 1_2}$= -7.8 kcal·mol^{-1}) is 3.5 kcal·mol^{-1} less stable than the corresponding **I2 1_4** ($\Delta G_{I2\ 1\_4}$= -11.3 kcal·mol^{-1}) and the formation of the product **P 1_2** ($\Delta G_{P\ 1_2}$= -10.3 kcal·mol^{-1}) is less favored than the formation of the **P 1_4** ($\Delta G_{P\ 1_4}$= -25.3 kcal·mol^{-1}). Thus, we only depict herein the 1,4-addition pathway for the TolS-Bpin and BnS-Bpin, which showed the same behavior.

The thiodioxaborolane BnS-Bpin seems to be again less reactive than the other two reagents by the fact that all the activation energies $\Delta G^{\neq}_{TS1}$, $\Delta G^{\neq}_{TS2\ 1\_4}$ and $\Delta G^{\neq}_{TS3\ 1\_4}$ are higher as well as the corresponding intermediates ΔG_{I1} and $\Delta G_{I2\ 1\_4}$. On the other hand, the computed values for the TolS-Bpin and PhS-Bpin pathways are very similar, being the TolS-Bpin slightly more reactive.



Scheme 3.17. Relative Gibbs Free Energies for the reaction pathway of the 1,2- and 1,4-addition of the RS-Bpin reagents to the substrate 4-phenyl-3-buten-2-one (**17**). All energies are in kcal·mol^{-1}.

We also computed the reaction pathway for the thioboration reaction of substrate 2-cyclohexenone (**33**) with PhS-Bpin. In this case the initial step based on the interaction of the carbonylic oxygen with the empty *p* orbital of the boron atom is the same as described above but after the first transition state **TS1** ($\Delta G^{\neq}_{TS1}$= 9.7 kcal·mol^{-1}) and the formation of the intermediate **I1** (ΔG_{I1}= 8.4 kcal·mol^{-1}), the 1,2-addition takes place trough a **TS2 1_2** ($\Delta G^{\neq}_{TS2}$= 18.1 kcal·mol^{-1}) giving the 1,2-addition intermediate **I2 1_2** (ΔG_{I2}= -9.5 kcal·mol^{-1}). However, and despite many efforts, the transition states corresponding to a direct 1,4-addition or an interconversion from 1,2 to 1,4-addition intermediates were not located. The *trans* disposition of the double bond in the substrate **33** seems to prevent the direct 1,4-addition because of geometric restrains.

It is worth mentioning that during the course of these investigations aimed at characterizing the evolution of the 1,2-addition intermediate, when we introduced water (or methanol) as protonation agents, the models evolved directly to the formation of the final 1,4 product and BpinOH (or BpinOMe). Thus, we think that the interconversion from 1,2 to 1,4-addition intermediates does not take place directly but it is coupled with the final protonation step. In any

case, our results justify the observation of the 1,2-addition intermediate in the reaction crude. A very recent report on phosphinoboration of aldehydes and *α,β*-unsaturated aldehydes has also proved the preferred 1,2-addition intermediates.[47]

3.4 Conclusions

The direct reactivity between the reagents ArY-Bpin (Y=Se, S, Ar=Ph, Tol) and activated olefins such as *α,β*-unsaturated ketones or aldehydes opens a new pathway towards the selective synthesis of *β*-phenylseleno and *β*-arylsulfido substituted carbonyl compounds. The substrate scope of the *α,β*-unsaturated ketones or aldehydes for this reaction is wide and includes cyclic and acyclic substrates (12 examples for the PhSe-Bpin).

This is a new methodology to achieve easily the C-Se and C-S bond formation in a selective way without any metal or organocatalyst assistance. Moreover, predictions are made on the reactivity of the sulphur and oxygen analogous. In addition, an experimental example of direct reaction between PhS-Bpin and 4-hexen-3-one (**25**) corroborates that selenium and sulfur follow the same pathway in the facile 1,4-addtion to *α,β*-unsaturated carbonyl compounds.

Based on our DFT studies, we propose a plausible mechanism of the reaction that explains the high selectivity towards the 1,4-addition products. Furthermore, nucleophilicity indexes have been calculated for the studied reagents, providing a prediction on the reactivity trend. Eventually, the pathway for the ArS-Bpin reagents has also been computed in order to confirm the similar trend.

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"To raise new questions, new possibilities,
to regard old problems from a new angle,
requires creative imagination
and marks real advance in science."

Albert Einstein

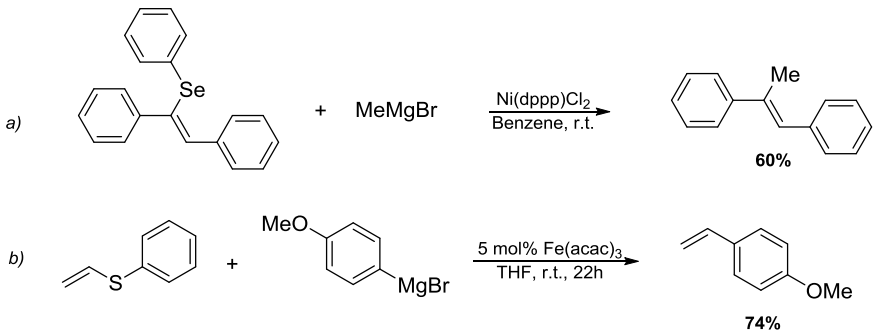
4. A theoretical approach to the metal-free synthesis of vinyl selenides and sulfides

Table of contents

UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

4.1 Introduction

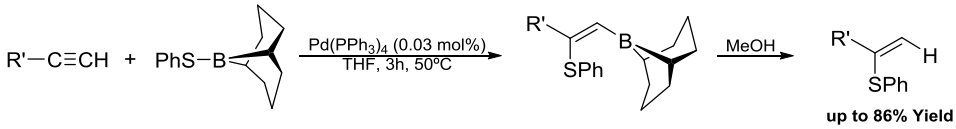
Vinyl chalcogenides[1] such as vinyl selenides and vinyl sulfides are compounds of great interest in organic synthesis due to their wide applicability in reactions such as cross coupling (Scheme 4.1),[2] sigmatropic rearrangements,[3] Diels-Alder reactions[4] among many other reactions. These compounds have also shown antioxidant properties.[5]



Scheme 4.1. a) Nickel- and b) Iron-catalyzed cross coupling of vinyl selenides and sulfides with Grignard reagents.

The synthesis of these reagents has been deeply covered from multicomponent perspectives with particular emphasis on the influence of transition metal complexes to generate the new C(sp^2)-Se and C(sp^2)-S bonds in a selective way.[6] Also DFT studies have been performed in order to understand the reaction mechanisms.[7]

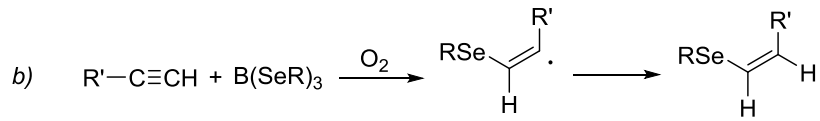
In that context, thioboration of alkynes with 9-(alkylthio)-9-borabicyclo[3.3.1]nonanes has been reported to take place in the presence of $Pd(PPh_3)_4$ in a regio- and stereo-selective way, which under subsequent protonolysis with methanol produces the Markovnikov adduct of thiol to alkynes (Scheme 4.2).[8]



Scheme 4.2. Suzuki's palladium-catalyzed thioboration of alkynes.

In a metal free context, the reaction of organoselenoboranes with acetylenes caused free radical 1,2-addition compounds (Scheme 4.3).[9] The synthesis of

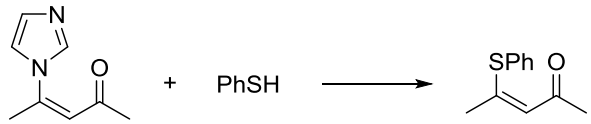
vinyl selenides and vinyl sulfides throughout chalcogenoborates has been limited to the previous examples despite the potential reactivity of these reagents.[10]



Scheme 4.3. Synthesis of vinyl selenides and vinyl sulfides throughout chalcogenoborates.

In particular, *β*-seleno and *β*-sulfido vinyl carbonyl compounds are remarkable due to their polifunctionality and potential use in further transformations and synthesis of complex molecules.[11]

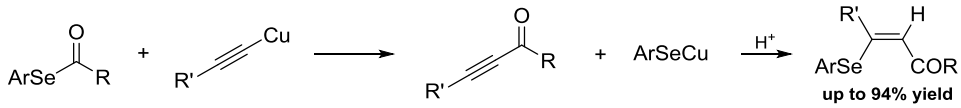
The first synthesis of these compounds was reported in 1982 by Omote and co-workers.[12] They achieved the reaction of 3-(1-imidazolyl)-2-alken-1-ones with several nucleophiles such as tiophenol in a 22% yield (Scheme 4.4).



Scheme 4.4. Addition of tiophenol to 3-(1-imidazolyl)-2-alken-1-ones.

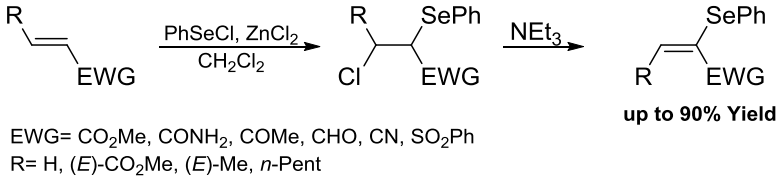
In 1987, Suama and co-workers reported the addition of thiols to conjugated allenic ketones and esters. Up to 93% yield of the products were obtained.[13]

Later on 1998 Meng and co-workers introduced the first selenocarbonylation addition reaction of selenoesters to nonactived terminal alkynes under the catalysis of CuX species. The reaction provided (*Z*)-*β*-arylseleno-*α,β*-unsaturated ketones in high yields and selectivity values.[14]



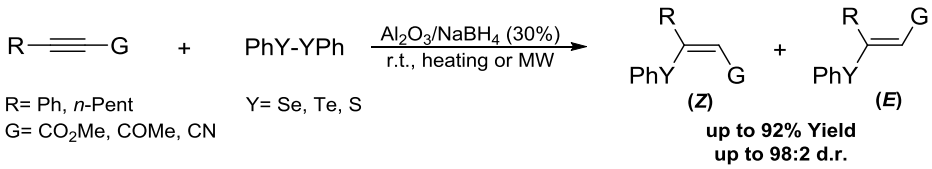
Scheme 4.5. Selenocarbonylation of selenoesters to non-activated alkynes.

In 2000, Berlin and Engman prepared in good yields *α*-phenylselenenyl-*α,β*-unsaturated esters, amides, ketones, nitriles and sulfones by zinc chloride promoted chloroselenation/dehydrochlorination of the corresponding *α,β*-unsaturated compounds (Scheme 4.6).[11]



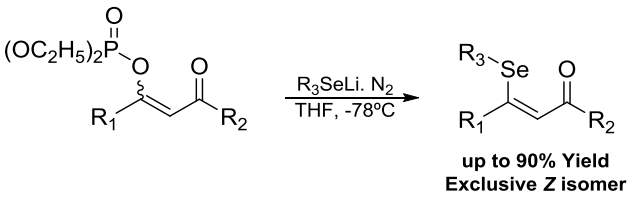
Scheme 4.6. Synthesis of *α*-phenylselenenyl-*α,β*-unsaturated esters, amides, ketones, nitriles and sulfones *via* chloroselenation/dehydrochlorination sequence.

More recently the synthesis of these compounds has been achieved throughout a clean and efficient solvent-free protocol for hydrochalcogenation of propargylic esters, ketones and nitriles. They used phenylchalcogenolate anions generated *in situ* from the respective diphenyl dichalcogenide (Se, Te, S), using alumina supported sodium borohydride. This method provided the respective (*Z*)-*β*-phenylchalcogeno-*α,β*-unsaturated esters, ketones and nitriles, in good yields (Scheme 4.7).[15]



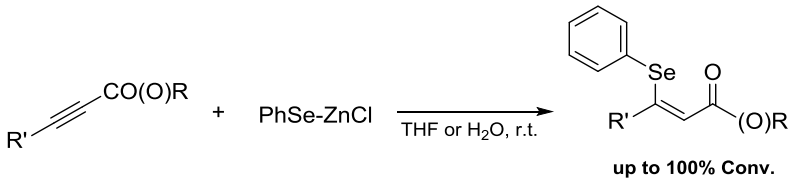
Scheme 4.7. Hydrochalcogenation of propargylic esters, ketones and nitriles.

Also in 2007, Comasseto and co-workers reported the reaction of enol phosphates of *β*-dicarbonyl compounds with lithium organoselenolates to give *β*-organoseleno (*Z*)-*α,β*-unsaturated carbonyl compounds (Scheme 4.8).[16]



Scheme 4.8. Reaction of enol phosphates with lithium organoselenolates.

In 2011, Santi and co-workers reported the Michael addition of the reagent PhSe-ZnCl to unsaturated ketones and electron-deficient alkynes, leading to synthetically useful *β*-seleno derivatives and vinyl selenides, respectively. The reactions were performed at room temperature in THF as well as in water and the reaction showed to be very selective towards the *Z* isomers (Scheme 4.9).[17]



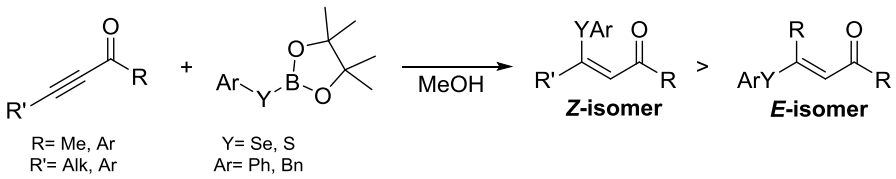
Scheme 4.9. Michael addition of PhSe-ZnCl reagent to propargylic ketones and esters.

4.2 Motivation

Bearing in mind that synthesis of vinyl selenides and vinyl sulfides is a not deeply explored field, and that most of the previously reported syntheses require metal catalysts and/or suffer from low yields and based on our recently acquired experience on the selenoboration and thioboration of vinyl carbonyl compounds:

Our group's aim was to efficiently promote the synthesis of vinyl selenides and vinyl sulfides in the absence of transition metal complexes or additives. To do so, we utilized the reagents PhSe-Bpin, TolS-Bpin, PhS-Bpin and BnS-Bpin to be added to propargyllic ketones (Scheme 4.10).

It is worth to mention that the experimental work of this project was utterly developed by my co-worker Marc Garcia. My personal aim in this chapter was to explore the reaction mechanism by means of DFT studies and to understand and justify the observed experimental trends.



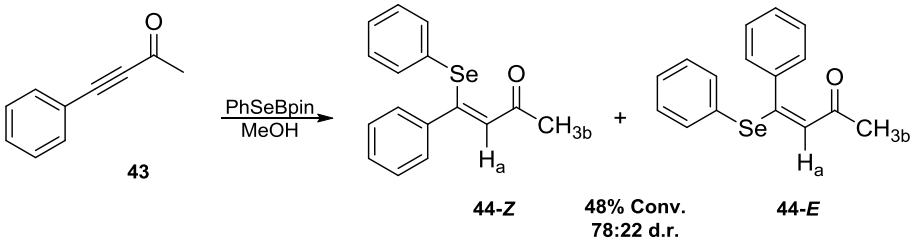
Scheme 4.10. Synthesis of vinyl selenides and vinyl sulfides throughout chalcogenoborates.

4.3 Results and discussion

4.3.1 Experimental results

As above mentioned, all the experimental work was performed by my co-worker Marc Garcia. The next section summarizes his experimental results to be compared with the theoretical results.

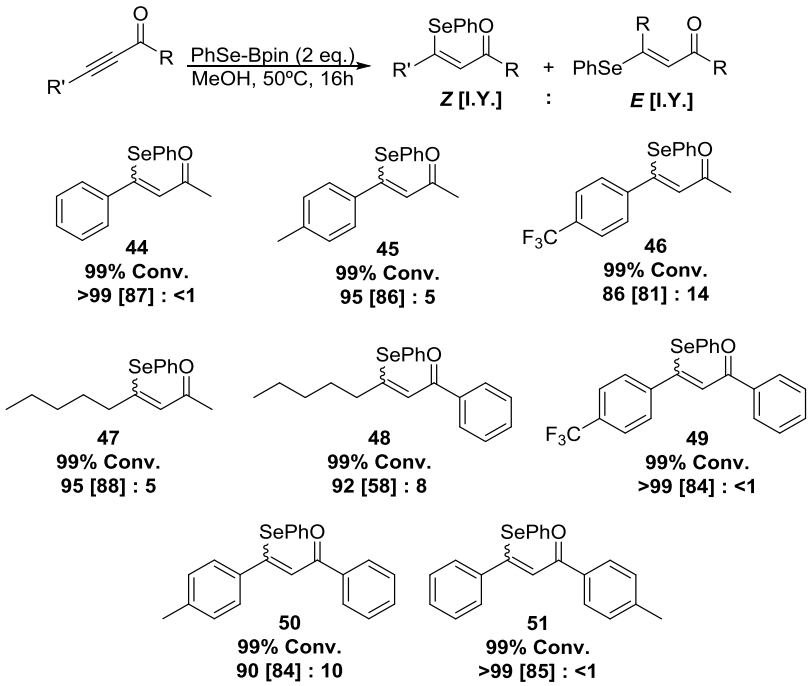
The addition of 1 eq. of PhSe-Bpin to the electron deficient alkyne 4-phenyl-3-butyn-2-one (**43**), in THF at 50 ºC for 16 hours provided the *β*-(phenylseleno)-*α,β*-unsaturated ketone **44** in 48% conversion with a diastereomeric ratio **44-*Z***/**44-*E***= 78/22 (Scheme 4.11).



Scheme 4.11. Reaction of the propargylic ketone **43** with PhSe-Bpin.

Both stereoisomers could be isolated and unequivocally characterized accordingly to NMR spectroscopy studies, and were assigned contrarily to Santi's previously reported data.[17]

The optimized reaction conditions included the use of MeOH as solvent and 2eq. of PhSe-Bpin to obtain complete conversion and total stereoselction towards **44-*Z*** after 16h of reaction at 50ºC. In total, 8 propargylic ketones (**45**-**52**) were successfully converted into the corresponding *β*-phenylseleno vinyl products (Scheme 4.12).



Scheme 4.12. Reaction of PhSe-Bpin with propargylic ketones. Scope of *β*-phenylseleno vinyl products.

Moreover, a single crystal of the product **51-*Z*** was obtained, confirming the *Z* configuration of the major stereoisomer, contrary to Santi's reported results[17] (Figure 4.1).

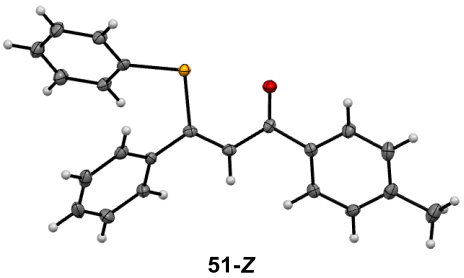
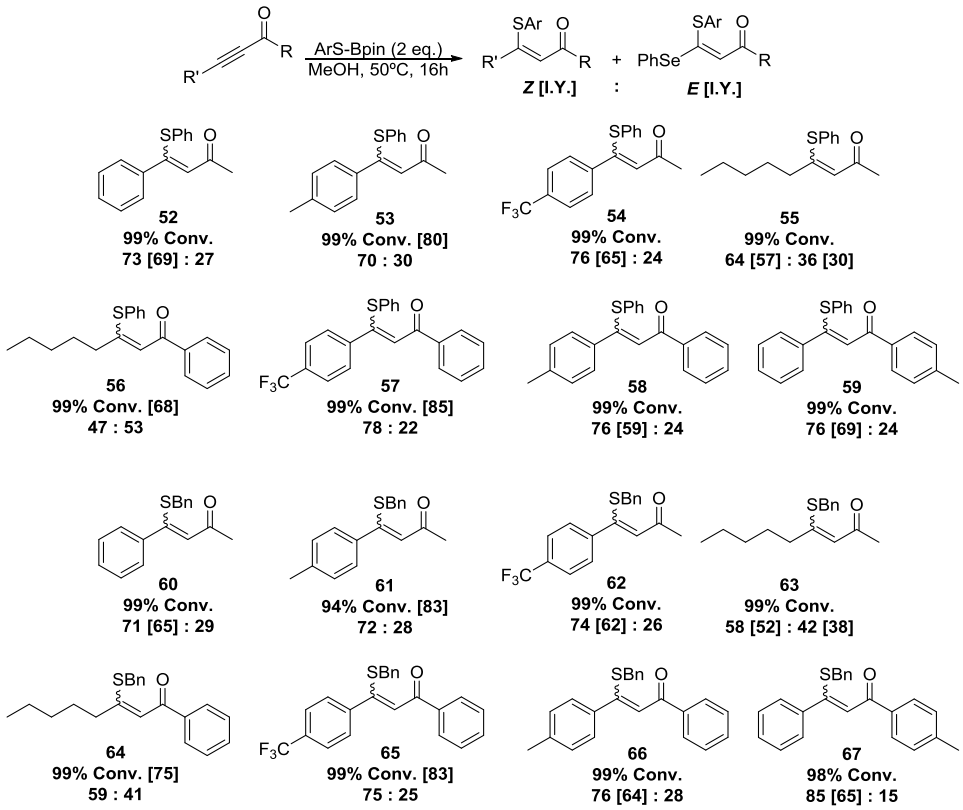


Figure 4.1. Ball and stick diagram of **51-*Z*** X-Ray structure

The next goal was to extend the same protocol to the chalcogenoborates PhS-Bpin and BnS-Bpin to synthesize vinyl sulfides from accessible ynones (Scheme 4.13). The same 8 substrates were successfully converted and the ArS was regioselectively added to the C_β position with a stereoselectivity

around *Z*/*E* = 3/1, independently of the nature of the Ar group in the thiodioxaborolane reagent.

The alkylic nature of the substituents in C_β seemed to favor the relative formation of the *E* isomer. The observed trend to form the (*Z*)-*α,β*-(arylsulfuro)-*α,β*-unsaturated ketone as the major isomer contrasts with alternative methodologies.[18] Most of the *Z* products could be successfully isolated in excellent yields but in some cases the products were isolated as a mixture of isomers (Scheme 4.13, products **53**, **56**, **57**, **61**, **64**, **65**).



Scheme 4.13. Reaction of the ArS-Bpin reagents with propargylic ketones. Scope of the reaction including conversion values, isolated yields and selectivity *Z*:*E* values.

4.3.2 DFT study

4.3.2.1 Computational details

All calculations were performed by using the Gaussian 09 package[19] with the hybrid M06-2X functional.[20] The standard 6–311G** basis set was used to describe the H, C, B, O, N and S atoms. Full geometry optimizations were per-

formed without constrains. The nature of the stationary points encountered was characterized either as minima or transition states by means of harmonic vibrational frequencies analysis. The zero-point, thermal, and entropy corrections were evaluated to compute enthalpies and Gibbs free energies (T=298 K, p=1 bar). Hydrogen atoms have been omitted for clarity in the graphic representation of the geometries. ^{1}H NMR isotropic chemical shifts[21] were computed doing single point calculations using the same functional, cc-pVTZ as basis set[22] and PCM model[23] for the solvation considering chloroform as solvent and reference.

4.3.2.2 NMR studies

We wanted to compute by DFT the ^{1}H NMR shifts of the obtained isomers of the product **44-*Z*** and **44-*E*** (Scheme 4.11) in order to compare them with the previously reported experimental values by Santi and co-workers (Table 4.1).[17] Again we observed that Santi's experimental results were more in accordance with the opposite computed stereoisomers. The computed vinylic protons appear slightly overshifted but the difference with the experimental values is similar for both cases ($\Delta\delta\approx$0.8-1.0 ppm) while the methyl protons are very well predicted ($\Delta\delta\approx$0.1-0.3 ppm). Thus, we were able to correct the previous NMR data assigned to **44-*Z*** which was isolated from the mixture of isomers **44-*Z*/44-*E*** = 66/34 after the addition of PhSe-ZnCl to 4-phenyl-3-butyn-2-one (**43**).[17]

Table 4.1. Comparison of the computed ^{1}H NMR shifts to the previously reported experimental values.[17]

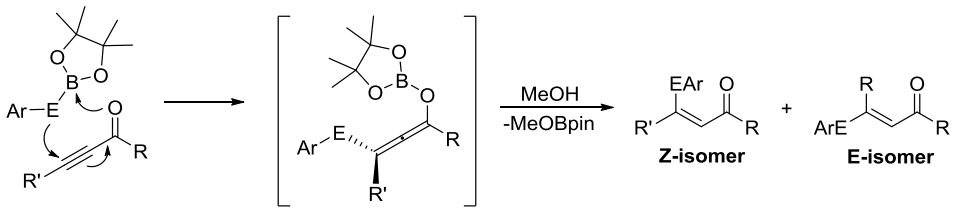
$$\delta H_{a\ Correction} = \delta H_{a\ Computed\ CDCl_3} - \delta H_{a\ Experimental\ CDCl_3}$$

$$\delta H_{n\ Corrected} = \delta H_{n\ Computed} + \delta H_{a\ Correction}$$

	$CDCl_3$	**Prod 44-*E***	**Prod 44-*Z***
$\delta H_{a\ Experimental}$	**7.26**	**6.83**	**5.94**
$\delta H_{a\ Computed}$	7.53	7.36	7.75
$\delta H_{a\ Correction}$	-0.27	-0.27	-0.27
$\delta H_{a\ Corrected}$	**7.26**	**7.09**	**7.48**
$\delta H_{b\ Experimental}$	-	**2.37**	**1.74**
$\delta H_{b\ Computed}$	-	1.73	2.55
$\delta H_{a\ Correction}$	-0.27	-0.27	-0.27
$\delta H_{b\ Corrected}$	-	**1.46**	**2.28**

4.3.2.3 Mechanistic proposal

Our mechanistic proposal started by considering the interaction of the carbonylic oxygen with the boron atom of the ArY-Bpin to activate the B-Y bond and facilitate the release of the nucleophilic ArY^- moiety that can attack the C_β of the substrate forming an allene intermediate that finally undergoes protonolysis to yield the corresponding products (Scheme 4.14).



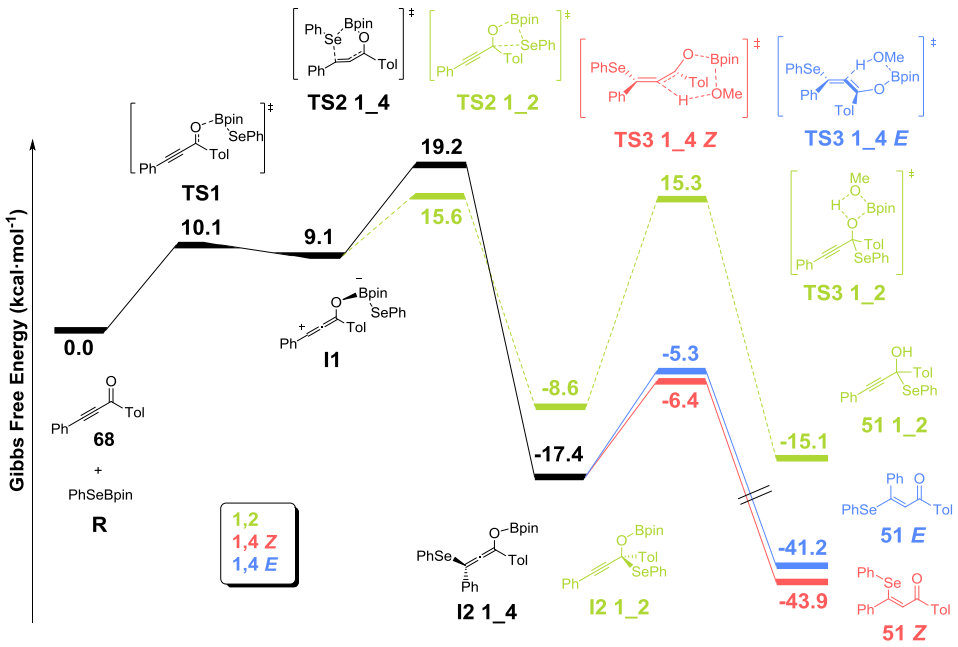
Scheme 4.14. Mechanistic proposal for the addition of ArY-Bpin to ynones.

By means of DFT we studied the Gibbs free energy profile for the reaction of the model alkyne 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**68**) with PhSe-Bpin (Scheme 4.15). It is important to note that this sort of substrates present two electrophilic points susceptible to be attacked by a nucleophile: The carbonyl group and the triple bond. Since the only experimentally observed products are the ones derived by the addition to the triple bond, we wanted to understand the selectivity of the reaction.

The activation of the PhSe-Bpin by the oxygen atom of the substrate occurs through a first transition step (**TS1**) and leads to the intermediate **I1**. Then, two pathways are possible: The attack of the nucleophilic $^-$SePh moiety to the carbonyl group (**TS2 1_2**) or to the triple bond (**TS2 1_4**). After the direct attack to the carbonyl takes place through the **TS2 1_2**, an intermediate **I2 1_2** is formed. This intermediate can finally undergo protonolysis with methanol to form the 1,2-addition product **51 1_2** and the byproduct MeO-Bpin(Scheme 4.15).

Considering the pathway for the Michael addition, after the **TS2 1_4** occurs, as we predicted, an allene intermediate is formed (**I2 1_4**). This intermediate can also undergo protonolysis with methanol by both faces, leading to two different transition states **TS3 1_4 *Z*** and **TS3 1_4 *E*** that give rise to the products **51 *Z*** and **51 *E*** respectively. Note that this **TS2 1_4** can also occur

by the other face of the substrate, giving rise to the other enantiomer of the **I2 1_4** that gives the energetically exact pathway (Scheme 4.15).



Scheme 4.15. Relative Gibbs free energies for the reaction pathway of the 1,2- and 1,4-addition of the PhSe-Bpin reagent to the model substrate 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**68**). All energies are in kcal·mol^{-1}.

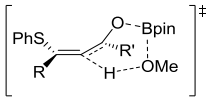
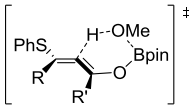
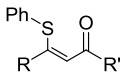
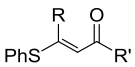
Our experimental results show that the obtained product for this reaction is exclusively the 1,4-addition product **51 *Z*** and no evidence of the formation of **51 *E*** isomer neither the 1,2-addition product **51 1_2** is observed. These results are in good agreement with our mechanistic proposal since the reaction pathway for the 1,2-addition is disfavored due to the lower stability of the intermediate **I2 1_2** and the high energy barrier for the **TS3 1_2** of the protonolysis ($\Delta G^{\neq}$=23.9 kcal·mol^{-1}). Moreover, the formation of the *Z* versus the *E* isomer is favorable both kinetically ($\Delta\Delta G^{\neq}$=1.1 kcal·mol^{-1}) and thermodynamically ($\Delta\Delta G$=2.7 kcal·mol^{-1}).

Next we also evaluated the effect on the selectivity of modifying partially the substrate with different propargylic moieties and using the two different sulphur homologous reagents PhS-Bpin and BnS-Bpin. At this point we observed no significant differences in energies between the results for both reagents. Next we computed the reaction pathway for the reaction of PhS-Bpin with the

substrates 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**68**) and 1-phenyl-2-octyn-1-one (**69**) in order to compare the energies of the most relevant species (Table 4.2).

In general terms, it can be observed that in both cases the transition state **TS3 1_4 *Z*** is lower in energy than its corresponding analogous **TS3 1_4 *E***. However, this energy difference is higher for the substrate **69** ($\Delta\Delta G^{\neq}$=6.0 kcal·mol^{-1}, Table 4.2, entry 2 vs 4) than for the substrate **68** ($\Delta\Delta G^{\neq}$=0.4 kcal·mol^{-1}, Table 4.2, entry 1 vs 3).

Table 4.2. Relative Gibbs Free energies for the crucial species involved in the selectivity of the reaction of alkynes **68** and **69** with PhS-Bpin. All energies are in kcal·mol^{-1}.

Species	Entry	Subst.	Δ*G*
 **TS3 1_4 *Z***	1	**68**	-5.3
	2	**69**	-7.7
 **TS3 1_4 *E***	3	**68**	-4.9
	4	**69**	-3.0
 **P 1_4 *Z***	5	**68**	-40.7
	6	**69**	-38.2
 **P 1_4 *E***	7	**68**	-39.7
	8	**69**	-40.6

Regarding the relative stability of the products, it can be observed that the products for the substrate **68** are very similar in energy ($\Delta\Delta G$= 1.0 kcal·mol^{-1}, Table 4.2, entries 5 vs 7) being the *Z* the most stable isomer. Nevertheless, for the substrate **69** the energy differences are higher ($\Delta\Delta G$= 2.4 kcal·mol^{-1}, Table 4.2, entry 6 vs 8) being in this case the *E* isomer the most stable.

In conclusion, the propargylic alkyl chain in the substrate seems to favor the *E* isomer thermodynamically but *Z* kinetically. As both activation energies for the **TS3 1_4** are not very high, they can be easily achieved, being rational the

obtaining of major proportion of the *E* isomer, as it is the most stable product. On the other hand, the phenyl group favors also kinetically the *Z* product but the energetic difference between the two **TS3** is much lower. The obtained products are much close in energy, what can justify the obtaining of mixtures enriched with the *Z* isomer.

Note also that comparing these obtained results for the substrate **68** with the ones obtained with the PhSe-Bpin reagent (Scheme 4.14), we observe the same trends, the *Z* isomer is both kinetically and thermodynamically favoured but the differences in energy between the two **TS3 1_4** transition states for the PhSe-Bpin reagent ($\Delta\Delta G^{\neq}$= 1.1 kcal·mol^{-1}) and between the two products ($\Delta\Delta G$= 2.7 kcal·mol^{-1}) are higher. This goes in accordance with the exclusive obtaining of the *Z* product for this reagent.

4.4 Conclusions

Once more, the powerful "pull-push" properties of Bpin units in the chalcogenoborate reagents PhSe-Bpin, PhS-Bpin and BnS-Bpin when reacting to propargylic ketones provides the synthetically very useful *β*-phenylseleno and *β*-arylsulfido vinyl products.

The computation of ^{1}H NMR shifts has been a useful and rather accurate tool which has allowed us to compare the predicted and experimental values to better assign the signals to the experimental products.

We have developed herein a DFT based mechanistic proposal that is able to justify the pathway towards of the *β*-vinyl selenides and sulfides and helps us to understand the selectivity of the reaction outcome as well as to explain the observed trends concerning different reagents and substrates.

4.5 References

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"Failure is simply the opportunity
to begin again, this time
more intelligently."

Henry Ford

5. An experimental approach to the metal-free selenolysis and thiolysis of epoxides

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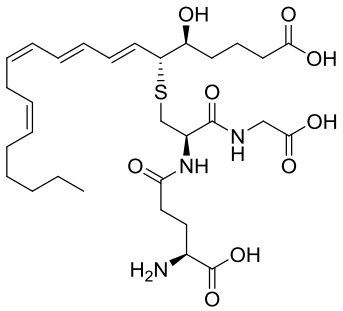
UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

5.1 Introduction

β-Hydroxy selenides and sulfides are an important class of organic intermediates[1] for constructing both synthetic pharmaceuticals[2] and naturally occurring substances[2a, 3] such as leukotrienes, pancratistatin,[4] and schweinfurthin B[5] (Figure 5.1).



Leukotriene LTC_4
inflammation agent

Figure 5.1. Leukotriene LTC_4, inflammation agent present in mouse mast cell tumor.

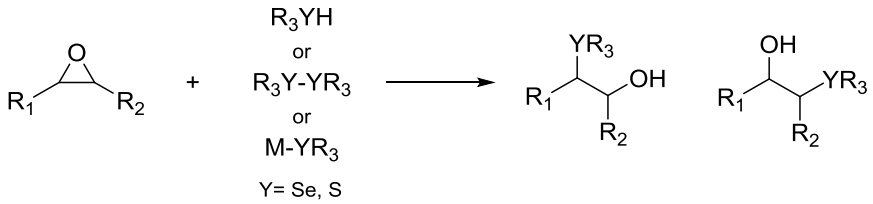
The selanyl group of *β*-hydroxy selenides can be used in radical carbon–carbon bond formation, especially the intramolecular type (radical cyclizations),[6] which is useful for synthesis of organic molecules.[7] *β*-Arylseleno alcohols are used as starting materials for several interesting synthetic applications.[8]

Due to their high importance, the synthesis of these compounds has been widely studied.

5.1.1 Synthesis of *β*-hydroxy selenides and sulfides

Tremendous research efforts have been devoted to the synthesis of *β*-hydroxy sulfides and selenides. These processes have been principally covered as a selenolysis or thiolysis of 1,2-epoxides.

While there are a few examples utilizing water or solvent-free conditions,[9] most examples involve toxic solvent and Lewis acid catalysts, such as tin complexes,[10] indium complexes,[11] $ZnCl_2$,[12] $AlPW_{12}O_{40}$,[13] gallium complexes,[14] lanthanide complexes,[15] $CoCl_2$,[16] $LiClO_4$,[17] AlR_3[18] scandium complexes[19] or titanium complexes.[20] Compared with the synthesis of *β*-hydroxy sulfides, less attention has been paid to the synthesis of *β*-hydroxy selenides by the ring-opening reaction of epoxides with ArSeH (Scheme 5.1).[21]



Scheme 5.1. General scheme for the selenolysis and thiolysis of epoxides.

Nowadays, reactions in aqueous medium have gained soaring popularity since water is inexpensive, non-toxic, safe, and environmentally benign as a solvent.[22] Known promoters for epoxide thiolysis in water include Brønsted acid (TsOH)[23], Brønsted base (NaOH,[24] in stoichiometric level), Lewis base (PBu_3,[25] DABCO and NEt_3[26]), and even microwave irradiation.[27] Some solvent-free examples for this reaction involved $Ga(OTf)_3$[28] and K_2CO_3[23] as catalysts. Other approaches include the use of ionic liquids[29] as solvents or heterogeneous supported catalysts.[30]

In spite of their respective features, the reported methods also suffer from the drawbacks in one way or another. For example, in most cases, thiolysis has to be carefully run at an appropriate pH value to ensure good regioselectivity and to minimize the side products resulted from hydrolysis[11b, 12] and/or double thiolysis[23] of the epoxides. The additives PBu_3 (air labile), DABCO, NEt_3, or K_2CO_3 catalyze the thiolysis but usually take long reaction time, ending up with unsatisfactory yields. Some metal catalysts are too expensive to be useful for large-scale production. Consequently, efficient and practical thiolysis of 1,2-epoxides remains a daunting challenge to contemporary organic chemists.

Other compounds such as cyanuric chloride, borax and N-bromosuccinimide (NBS) were reported in 2008 by Sawant[31], Zhai[32] and Hadi[33] respectively for the efficient ring opening of epoxides with thiols. Short reaction time, mild reaction conditions, inexpensive and readily available catalysts, provided excellent yields of the desired products under solvent-free conditions (Figure 5.2).

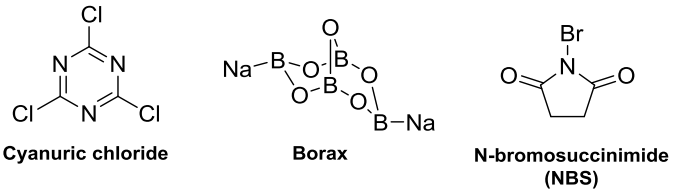
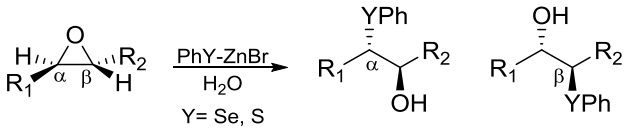


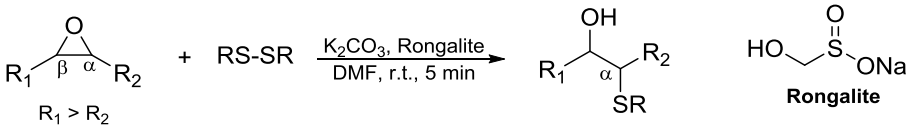
Figure 5.2. Some agents utilized on the mild thiolysis of epoxides.

In 2008 Santi and co-workers reported the synthesis of a new bench-stable and odorless zinc selenolate used in the selenolysis of epoxides. This reagent showed a considerable rate acceleration of the reaction when effected in "*on-water*" conditions. In addition, the reactions provided a good regioselectivity when combining organic solvents with Lewis acid catalysis.[34] Also, in 2013 they developed the same sort of reagent for the thiolysis of epoxides (Scheme 5.2).[35]



Scheme 5.2. On water synthesis of *β*-hydroxy selenides and sulfides.

Chandrasekaran[36] and Wu (Scheme 5.3)[37] reported simultaneously that diaryl disulfides and diselenides undergo facile cleavage on treatment with rongalite (sodium hydroxyl-methanesulfinate) to generate *in situ* the corresponding thiolate and selenolate species, which cause the ring opening of aziridines and epoxides in a regioselective manner.

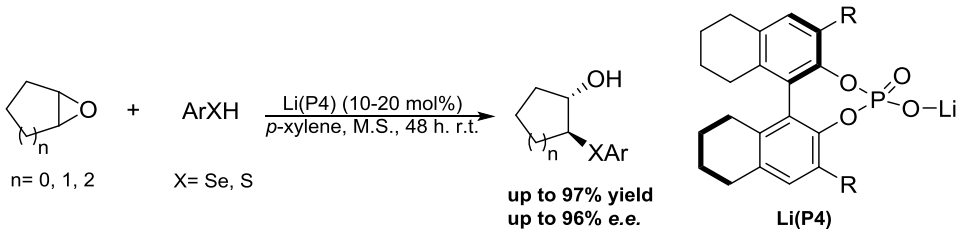


Scheme 5.3. Rongalite-mediated ring opening of epoxides with thiols.

In 2010 several advances in the field were reported. LiOH,[38] $MgCl_2$[39] and Cu/MgO[40] showed to be efficient catalysts for a mild ring opening of epoxides with thiophenol and its derivatives. In most cases, the reactions were performed at room temperature and in solvent-free conditions to afford the corresponding *β*-hydroxy sulfides.

In 2014 Khalili and co-workers reported an environmentally friendly and efficient procedure for the ring opening of various epoxides with thiols under non-thermal conditions. Ultrasonic irradiation of the two reactants suspended in an additive-free aqueous medium leads to the high-yield formation of various *β*-hydroxy sulfides is quickly observed.[41]

Also last year Antilla and co-workers presented a highly enantioselective method for desymmetrization of *meso*-epoxides using thiols and selenols. This was the first example of epoxide activation achieved using metal BINOL phosphates. The reaction has a broad scope in terms of epoxide substrates and aromatic thiol nucleophiles. The resulting *β*-hydroxyl selenides and sulfides are obtained in excellent yields and enantioselectivities (Scheme 5.4).[42]



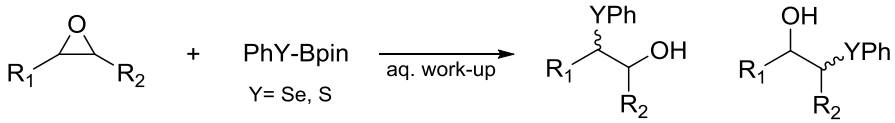
Scheme 5.4. Desymmetrization of meso-epoxides with thiols and selenols.

Chihara and co-workers have recently reported a series of molecular rhenium sulfide clusters $K_4[Re_6S_8Cl_6]$, $K_4[Re_6S_8(OH)_6]$, and $[Re_6S_8(H_2O)_6]SO_4$ supported on silica gel able to catalyze ring-opening addition of thiols to epoxides to yield *β*-hydroxy sulfides in gas-phase.[43]

Several organoselenides have been prepared as well by means of biocatalysis.[44] This methodology afforded enantiopure organoselenium compounds.

5.2 Motivation

Since the metal-free selenolysis and thiolysis of epoxides is not a widely explored field, and having succeeded in the reaction of PhSe-Bpin and ArS-Bpin with *α,β*-unsaturated substrates; we envisaged the synthesis of *β*-hydroxy selenides and sulfides by the reaction of ArY-Bpin with epoxides (Scheme 5.5).



Scheme 5.5. General scheme of the expected reaction of ArY-Bpin with epoxides.

Also, we wanted to perform some DFT studies in order to understand the reaction outcome.

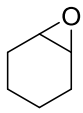
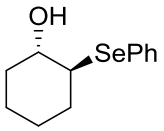
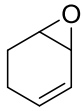
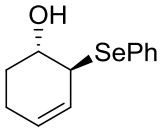
5.3 Results and discussion

5.3.1 Experimental results

Based on our experience, our initial experiment was to test the reaction of 1.1 eq. of PhSe-Bpin with the epoxide epoxycyclohexane (**70**), in THF at room temperature. We observed two new very significant multiplets in the ^{1}H NMR spectroscopy at 3.30 and 2.79 ppm (corresponding to the neighbor protons to the alcohol and selenide groups respectively) as well as a broad singlet at 2.98 ppm (corresponding to the OH proton). Comparing the obtained spectra to the previously reported,[21d, 45] we were able to identify the *trans* isomer of the *β*-hydroxy phenylselenide **71**, which was obtained in 36% of conversion (Table 5.1, entry 1).

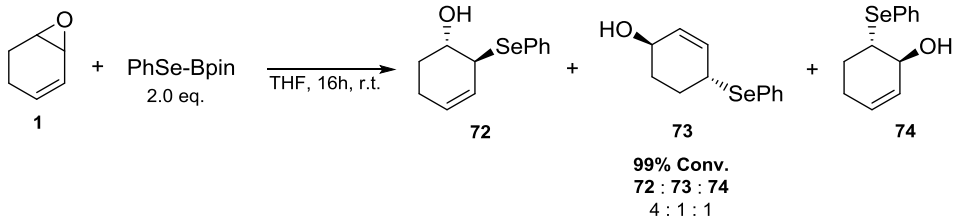
We next proceeded to the optimization of the reaction conditions. We observed that an increment of the temperature to 50 ºC had a negative effect on the conversion (Table 5.1, entry 2) whilst an increment of the amount of PhSe-Bpin reagent to 2.0 equivalents yielded to almost total conversion from the substrate **70** towards the product **71** (Table 5.1 entry 3). Eventually we were able to isolate and characterize the product **71** by NMR in high isolated yield.

Table 5.1. Optimization of the reaction conditions of the reaction of PhSe-Bpin with substrates **70** and **1**.

Entry	Substrate	Eq. PhSe-Bpin	Temp (ºC)	Product[b]	Conv.	I.Y.
1		1.1	25		36	10
2		1.1	50		21	16
3	**70**	2.0	25	**71**	91	81
4[a]		1.1	25		45	18
5		1.1	25		75	34
6		2.0	25		99	21
7	**1**	1.1	50	**72**	98	12

Optimized reaction conditions: The products were obtained by mixing the substrate (0.3 mmol) with the reagent PhSe-Bpin in THF (3 mL) overnight at room temperature. a) 6 hours of reaction time. b) Unique or major obtained product.

Next we moved to a more challenging substrate, 3,4-epoxy-1-cyclohexene (**1**) and we performed the reaction with 1.1 equivalents of PhSe-Bpin at room temperature for 6 hours (Table 5.1, entry 4). As expected, a mixture of products that we could identify by two-dimensional NMR was obtained, since the substrate has three electrophilic points susceptible to be attacked (Scheme 5.6). We observed that the major product **72** comes from the attack to the epoxide carbon in α to the double bond and it also is formed as the *trans* isomer.



Scheme 5.6. Reaction of the substrate **1** with PhSe-Bpin.

We observed that an increase of the reaction time from 6 to 16 hours was beneficial and that both an increment of the temperature to 50 ºC and the amount of reagent to 2.0 equivalents meant total conversion of the substrate, even though the selectivity was not improved. (Scheme 5.6, Table 5.1 entries

4-7). Thus, we selected 16 hours, room temperature and 2.0 equivalents of the reagent as the best reaction conditions.

Then, our aim was to extend the substrate scope for this reaction and we successfully achieved up to 6 cyclic and non cyclic substrates. We isolated each product to obtain the corresponding isolated yield values (Figure 5.3).

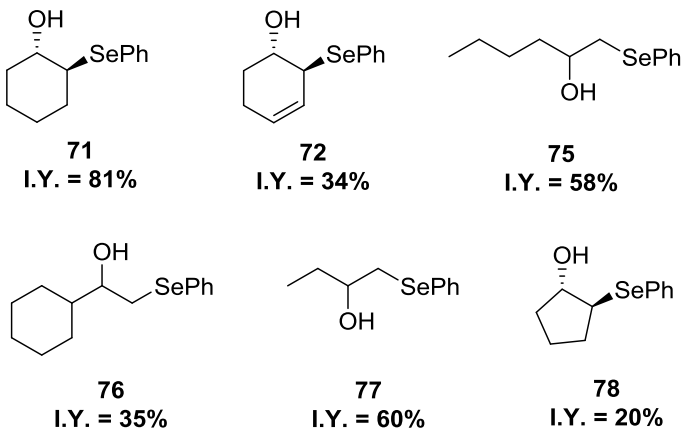


Figure 5.3. Substrate scope of the reaction of PhSe-Bpin with epoxides.

In all cases, isolated yields were low to moderate presumably due to low conversion values and a partial loss of the product by the silica purification. Also, we found some problems in the reproducibility of the reaction, being sometimes unable to obtain the same results when repeating exactly the same reaction. We also tested different solvents such as MeOH and higher temperatures but the results did not improve in any case.

We next moved to the reagent PhS-Bpin and we tried the same reaction conditions as the previous reactions. We observed the expected same reactivity for all substrates but we were not able to isolate the PhS analogous of **78**. Also in this case we had the same problems of reproducibility and with the purification.

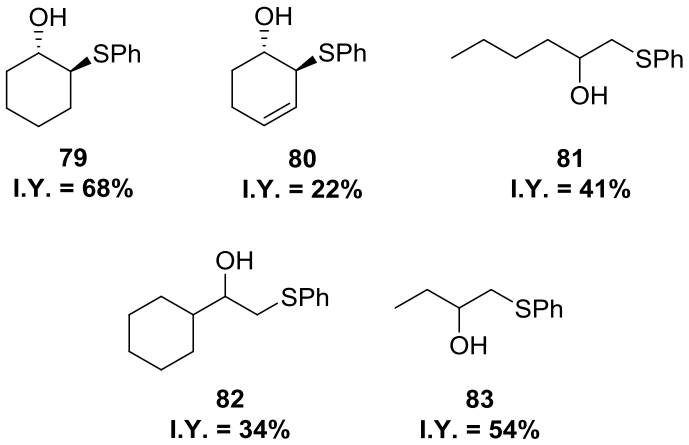


Figure 5.4. Substrate scope of the reaction of PhS-Bpin with epoxides.

Unfortunately at this point we found our limitation on the substrate scope, since we unsuccessfully tried the reaction of up to 12 other cyclic and non cyclic substrates with these reagents and we obtained no conversion.

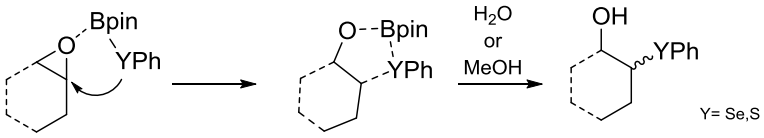
5.3.2 DFT study

5.3.2.1 Computational details

All calculations were performed by using the Gaussian 09 package[46] with the hybrid M06-2X functional.[47] The standard 6–311G** basis set was used to describe the H, C, B, O, N and S atoms. Full geometry optimizations were performed without constrains. The nature of the stationary points encountered was characterized either as minima or transition states by means of harmonic vibrational frequencies analysis. The zero-point, thermal, and entropy corrections were evaluated to compute enthalpies and Gibbs free energies (T=298 K, p=1 bar). Some hydrogen atoms have been omitted for clarity in the graphic representation of the geometries.

5.3.2.2 Mechanistic proposal

Our initial mechanistic proposal consisted in the activation of the PhY-Bpin reagent by the substrate. We suggested that this process might occur through the interaction of the oxygen atom of the epoxide with the boron atom of the reagent to be next followed by the attack of the nucleophilic PhY^- moiety to the oxirane ring that would lead to the ring opening (Scheme 5.7). After hydrolysis or methanolysis, the final product is expected.



Scheme 5.7. Initial mechanistic proposal for the reaction.

We proceeded to compute the first step of the mechanism, that is the interaction between the epoxide and the PhSe-Bpin reagent. We found out a first transition state **TS1** ($\Delta G^{\neq}$= 9.9 kcal·mol^{-1}) that lead to a first intermediate **I1** (ΔG_{I1}= 9.7 kcal·mol^{-1}) consisting on a substrate-reagent adduct. This adduct is very similar to the **I1** species that we found in the previous chapters for the substrate-reagent coordination (Figure 5.6).

Next we found a transition state **TS2** corresponding to the ring opening of the oxirane ring (α= 87.62º) with a still quite long Se-C distance (d_{Se-C}= 3.19 Å). Moreover, the negative frequency does not seem correspond to the attack of the selenium moiety to the electrophilic carbon. Next, we found out that this **TS2** leads to the formation of the intermediate **I2** and the attack seems to be barrierless since we were could not find a next TS corresponding to this process (Figure 5.6). The last step of the reaction would be the hydrolysis of this **I2** to form the final product.

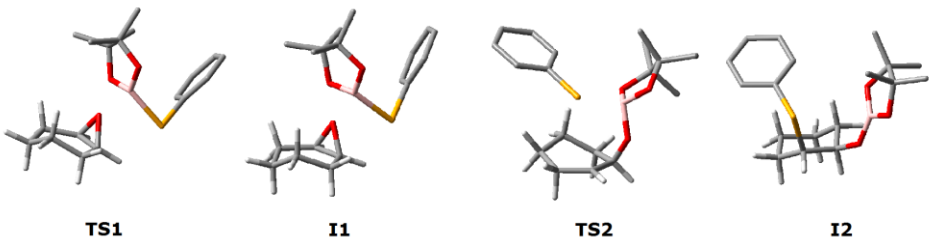


Figure 5.5. Graphical representation of computed geometries of the involved species.

It is important to mention that the orientation of the oxygen, boron and selenium atoms in **TS2** leads to a *syn* attack of the selenium moiety that finally yields the formation of the *cis* isomer of the intermediate **I2** (Figure 5.6).

Despite our big efforts, we were not able to locate a **TS2-*anti*** that would lead to the *trans* intermediate **I2-*trans***, which after protonolysis becomes the *trans* product (the only observed isomer). Therefore, our mechanistic proposal

was not consistent with the experimental results. We attribute this fact to three main possible reasons:

Probably there is a limitation in our method, since we did not take into account some important factors such as the explicit presence of the THF solvent molecules that might play a role for instance, interacting with the reagents; although we utilized the PCM continuous model during the unsuccessful search of the **TS2-*anti***. We did not either consider the high concentration values of the substrate and the reagent or the stoichiometry of the reaction.

On the other hand, there might be another operating reaction mechanism that yields the *trans* instead of the *cis* isomer. Since after the **TS2** the $PhSe^-$ moiety is released, a plausible explanation for the obtaining of the *trans* isomer would be the subsequent attack of this moiety to the less hindered lower face of another substrate molecule. This fact is also supported by the obtaining of a mixture of products when the substrate is less symmetrical, such as substrate **1** (Scheme 5.6). The fact that the products **73** and **74** are formed can be justified by the attack of a free $PhSe^-$ nucleophile, given that if the attack was directed by the O-B-Se interaction, it would never be possible to obtain the *trans* isomer of the product **73**.

Another possible explanation arises from the total lack of awareness about the protonolysis process, where complex mechanisms involving protic agents might occur, leading to obtained *trans* isomers.

5.4 Conclusions

We successfully extended the use of the reagents PhSe-Bpin and PhS-Bpin to the selenolysis and thiolysis of epoxides in absence of any additive. Very mild reaction conditions provided the SN_2 products that could be isolated in low to moderate yields. The reaction was selective to the *anti* products and the nucleophilic moiety attacked to the terminal epoxide carbon.

Moreover, the reaction seems to be comparable with both the PhSe-Bpin and PhS-Bpin reagents and remarkably gives only the *anti* product in all cases. As expected, the use of vinyl epoxides has provided mixtures of the SN_2 and SN_2' products.

This methodology opened a non-existing pathway towards the synthesis of *β*-hydroxy selenides and sulfides in a metal-free context. However, we found the limitation in the small reaction scope available to this transformation, after having obtained no conversion for 12 substrates.

In addition, we performed DFT studies to unravel the reaction mechanism even though we were not able to find a **TS2-*anti*** that after hydrolysis, would lead to the *trans* isomer of the product. Thus we suggest that after the release of the $PhSe^-$ moiety, an attack of this moiety to the lower face of another substrate molecule might occur.

Also this fact can be caused by a limitation in our method, since we did not take into account explicitly the presence of solvent molecules or factors such as concentration or stoichiometry.

The total ignorance of the mechanism that operates during the protonolysis process opens the doors to alternative mechanisms that might lead to the *anti* isomer.

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THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
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6. Conclusions

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6.1 *Chapter 2*. Metal-free borylative ring opening of vinyl epoxides and aziridines

We have developed a methodology for the metal-free borylative ring opening of vinyl epoxides and vinyl aziridines. This is an extension of our group's previous works on the metal-free borylation reactions of activated and non activated alkenes. The sole addition of B_2pin_2 with a base and MeOH provides *in situ* the $[B_2pin_2 \cdot OMe]^-$ adduct formation. As a consequence of this Lewis acid-base interaction, the sp^2 Bpin moiety acquires an enhanced nucleophilic character that allows the attack at the conjugated C=C of vinyl epoxides and aziridines, throughout a S_N2' pathway. The reaction took place exclusively on the contrary face of the oxirane or aziridine ring, giving rise to the *anti* borylated products. Further derivatization of the allylboronate products via oxidation or reactivity with benzaldehyde has allowed us to confirm the stereostructures.

From a theoretical point of view, we have proposed a plausible mechanism for the metal-free borylation of cyclic and non-cyclic vinyl epoxides and aziridines. The mechanism is in accordance with our experimental results and helps to understand the role of each reagent in the reaction.

6.2 *Chapter 3*. Novel synthesis of *β*-seleno and *β*-sulfido carbonyl compounds

In this chapter we have explored the direct reactivity between the reagents ArY-Bpin (Y=Se, S, Ar=Ph, Tol) and vinyl ketones and aldehydes. This represents a new and selective methodology towards the synthesis of *β*-phenylseleno and *β*-arylsulfido substituted carbonyl compounds. The substrate scope of the *α,β*-unsaturated ketones or aldehydes for this reaction is wide and includes cyclic and acyclic substrates (12 examples for the PhSe-Bpin).

This is a new methodology to achieve easily the C-Se and C-S bond formation in a selective way without any metal or organocatalyst assistance. Moreover, predictions are made on the reactivity of the sulphur and oxygen analogous. In addition, an early experiment of direct reaction between PhS-Bpin and 4-hexen-3-one (**25**) corroborates that selenium and sulfur follow the same pathway in the facile 1,4-addtion to vinyl carbonyl compounds.

Based on our DFT studies, we propose a plausible mechanism of the reaction that explains the high selectivity towards the 1,4-addition products. Moreover, nucleophilicity indexes have been calculated for the studied reagents, providing a prediction on the reactivity trend. Eventually, the pathway for these ArS-Bpin reagents has also been computed in order to confirm the similar trend.

6.3 *Chapter 4*. A theoretical approach to the metal-free synthesis of vinyl selenides and sulfides

Once more, the powerful "pull-push" properties of Bpin units in the chalcogenoborate reagents PhSe-Bpin, PhS-Bpin and BnS-Bpin when reacting to propargylic ketones provides the synthetically very useful *β*-phenylseleno and *β*-arylsulfido vinyl products.

The computation of ^{1}H NMR shifts has been a useful and rather accurate tool which has allowed us to compare the predicted and experimental values to better assign the signals to the experimental products.

We have developed herein a DFT based mechanistic proposal that is able to justify the pathway towards the *β*-vinyl selenides and sulfides and helps us to understand the selectivity of the reaction outcome as well as to explain the observed trends concerning different reagents and substrates.

6.4 *Chapter 5*. An experimental approach to the metal-free selenolysis and thiolysis of epoxides

We successfully extended the use of the reagents PhSe-Bpin and PhS-Bpin to the selenolysis and thiolysis of epoxides in absence of any additive. Very mild reaction conditions provided the SN_2 products that could be isolated in low to moderate yields.

Moreover, the reaction seems to be comparable with both the PhSe-Bpin and PhS-Bpin reagents and remarkably gives only the *anti* product in all cases. The use of vinyl epoxides provided mixtures of the SN_2 and SN_2' products.

This methodology opened a non existing pathway towards the synthesis of *β*-hydroxy selenides and sulfides in a metal-free context.

In addition, we performed DFT studies to propose a plausible mechanism but we were not able to find a **TS2-*anti*** that after hydrolysis, would lead to the *trans* isomer of the product. Thus we suggest that after the release of the $PhSe^-$ moiety, an attack of this moiety to the lower face of another substrate molecule might occur.

Also this fact can be caused by a limitation in our method, since we did not take into account explicitly the presence of solvent molecules or factors such as concentration or stoichiometry.

The total ignorance of the mechanism that operates during the protonolysis process opens the doors to alternative mechanisms that might lead to the *anti* isomer.

7. Experimental part

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7.1 General considerations

Unless otherwise mentioned, all reactions and manipulations were carried out under argon atmosphere using Schlenk-type techniques and oven-dried (120 ºC) glassware, which was cooled in a stream of argon. Solvents were dried using a solvent purification system (Pure SOLV system-4). Dry tetrahydrofuran (THF) supplied by PANREAC was purified in a MBRAUN MB-SPS-800 solvent purification system before using. Methanol was distilled over CaH_2. Unless specified, substrates were purchased from Sigma-Aldrich or Alfa Aesar and used as received. The reagents PhSe-Bpin, PhS-Bpin, TolS-Bpin, BnS-Bpin were fully synthesized and stored in the glovebox. All the chemicals were handled using standard chemical techniques using safety glasses, laboratory coat and gloves.

Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements. NMR spectra were obtained using VARIAN Mercury spectrometer VX400 and Varian NMR System 400. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane, referenced to the chemical shift of residual solvents resonances. $^{11}B\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to $BF_3{\cdot}OEt_2$ (δ $^{11}B\{^{1}H\}$ = 0.00 ppm) as the external reference. Coupling constants (*J*) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

GC was equipped with column HP-5.
Initial temp: 80ºC, initial time: 3 min.
Rate: 20ºC/min
Pressure: 100 kPa
Temp. injector: 225ºC
Temp. detector: 250ºC

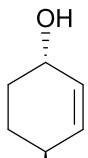
GC-MS was equipped with a HP-5MS capillary column (30m x 0.25 mm x 0.25 mm). Accurate mass determinations were carried out on a Kratos Concept IS spectrometer. MS (70 eV); m/z: (M^+). The same GC method was utilized.

7.2 Metal-free borylative ring opening of vinyl epoxides and aziridines

7.2.1 General procedures for the metal-free borylative ring opening of vinyl epoxides and aziridines with B_2pin_2

Borylation of 3,4-epoxy-1-cyclohexene (**1**)

Organocatalytic borylation: The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and B_2pin_2 (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate **1** (33 µL, 0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at room temperature for 6 hours. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR showing that one single product was formed from the substrate. The obtained 4-cyclohexenyl hydroxyboronate (**2**) was purified by flash chromatography using a silica gel column previously deactivated with triethylamine, and a mixture of petroleum ether and ethyl acetate (10:3) as eluent (R.f.=0.35). The product **2** could be isolated in 41.7 mg (62% yield).



2

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.88 (dd, J= 10, 2.8 Hz, 1H), 5.71 (dt, J=10, 2.6 Hz, 1H), 4.18 (s, 1 H), 1.88-1.76 (m, 2 H), 1.73-1.52 (m, 3 H), 1.21 (s, 6 H), 1.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 131.72, 128.61, 83.66, 65.47, 32.06, 25.29, 25.04, 24.91, 20.50

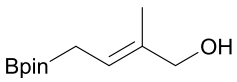
^{11}B NMR (128.52 MHz, $CDCl_3$) δ (ppm): 33.26.

Copper mediated borylation: CuCl (1.5 mg, 0.015 mmol), 1,3-Bis(diphenylphosphino)propane (dppp) (13 mg, 0.03 mmol), cesium carbonate (2 eq.) and B_2pin_2 (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the borane reagent completely. The substrate **1** (33 µL, 0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at room temperature for 6 hours. An ali-

quot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H NMR.

Borylation of 2-methyl-2-vinyloxirane (**7**)

The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and B_2pin_2 (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate **7** (33 µL, 0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at 50ºC for 20 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to probe that one single product was formed from the substrate. The obtained 2-methyl-4-pinacolboryl-butenol (**8**) was purified by flash chromatography using a silica gel column previously treated with triethylamine, and a mixture of petroleum ether and ethyl acetate (1:1) as eluent (R.f.=0.42). The product could be isolated in 42.0 mg (66% yield).



8

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.51 (t, J= 8 Hz, 1H), 4.40 (bs, 1H), 4.00 (s, 2H), 1.70 (s, 3H), 1.65 (d, 2H), 1.21 (s, 6H). 1.16 (s, 6H).

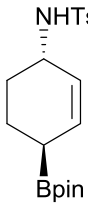
^{13}C NMR (100 MHZ, $CDCl_3$) δ (ppm) 134.86, 121.34, 83.24, 69.20, 24.74, 18.61, 13.62.

^{11}B NMR (128.52 MHz, $CDCl_3$) δ (ppm) 33.41

Borylation of 3,4-aziridine-1-cyclohexene (**10**)

The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and B_2pin_2 (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate **10** (0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at 50ºC for 20 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to probe that one single product was formed from the substrate. The obtained 1,4-cyclohexenyl tosylaminoboronate (**11**)

was purified by flash chromatography using a silica gel column previously treated with triethylamine, and a mixture of petroleum ether and ethyl acetate (7:3) as eluent (R.f.=0.49). The product could be isolated in 80.3 mg (71% yield).



11

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J*= 8.0 Hz), 5.82-5.79 (m, 1H), 5.30-5.26 (dt, 1H, *J* = 9.8, 3.5 Hz,), 4.41 (d, 1H, *J* = 8.0 Hz), 3.79 (br s, 1H), 2.43 (s, 3H), 1.52-1.90 (m, 5H), 1.20 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.2, 138.3, 132.4, 129.6, 127.0, 125.4, 83.4, 48.8, 30.1, 25.0, 24.7, 24.6, 21.6, 20.6.

^{11}B NMR (128.52 MHz, $CDCl_3$) δ (ppm): 33.44.

Spectral data is in accordance with the literature.[1]

Borylation of 2-methyl-2-vinylaziridine (**13**) and 3-methyl-2-vinylaziridine (**14**)

The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and B_2pin_2 (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate mixture (0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at 50ºC for 20 hours. The reaction mixture was next cooled to room temperature.

7.2.2 General procedure for the aziridination of dienes

The substrates 3,4-aziridine-1-cyclohexene (**10**), 2-methyl-2-vinylaziridine (**13**) and 3-methyl-2-vinylaziridine (**14**), were prepared following the methodology established in the literature.[2]

PhI=NTs (1 mmol) was added portionwise to a stirred solution of freshly distilled diene (2.02 mmol) and $Cu(acac)_2$ (27 mg, 0.1 mmol) in CH_3CN (2 mL) at 0°C under N_2. After being stirred for 15 min, the reaction was allowed to warm to rt and stirred for a further 45 min. Then, the reaction mixture was poured into NaOH (aq) (1 M, 20 mL). Et_2O (5 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL), and the

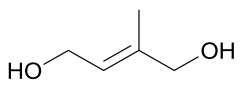
combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give the corresponding cyclic aziridines in 45-80% yield.

7.2.3 The oxidation protocol

The allyl boronates obtained in the above described procedure were converted into the corresponding alcohols in the following manner. To the crude organoboron product (cc. 0.3 mmol) in THF (3 mL), sodium perborate (90 mg, 0.9 mmol) and water (3 mL) were added. The reaction mixture was stirred vigorously overnight at room temperature. The reaction mixture was diluted with water and then extracted with dichloromethane (3 x 20mL). The combined organic phase was dried over $MgSO_4$ and concentrated.

Product **3** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.70). The product could be isolated in 32.5 mg (95% yield). Spectral data is in accordance with the literature.[3]

Product **9** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.52). The product could be isolated in 26.7 mg (87% yield).

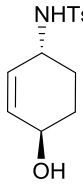


9

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.70-5.65 (tq, 1H, J= 6.8, 1.6 Hz), 4.24-4.22 (d, 2 H, J= 6.8 Hz), 4.01 (s, 2 H), 1.71 (s, 3 H).

^{13}C NMR (100 MHZ, $CDCl_3$) δ (ppm) 138.87, 124.14, 68.41, 59.47, 30.14.

Product **12** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.75). The product could be isolated in 72.2 mg (90% yield).



12

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 5.78-5.74 (d, 1H J = 10 Hz), 5.45-5.43 (d, 1H J = 10 Hz), 4.48 (d, 1H), 4.18 (m, 1H), 3.88-3.84 (m, 1H), 2.44 (s, 3H), 2.04-1.95 (m, 3H), 1.35-1.50 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.5, 138.1, 134.1, 129.9, 126.9, 65.6, 49.6, 30.7, 28.7, 21.6.

Spectral data is in accordance with the literature.[1]

Products **15/16** were purified as a mixture of diols by flash chromatography utilizing a silica gel column with ethyl acetate as eluent (R.f.=0.56). The products could be isolated in 30.6 mg (40% yield).

7.2.4 Allylation reaction of allyl boronates with benzaldehyde

The allyl boronates **2** and **5** obtained in the organocatalytic and copper mediated borylation, respectively, were derivatized with benzaldehyde. To the crude organoboron product (cc. 0.3 mmol) in THF (3 mL), benzaldehyde (100 µL, 0.9 mmol) was added. The reaction mixture was stirred vigorously overnight at room temperature. Product **4** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.80). The product could be isolated in 56.4 mg (92% yield). Product **6** was purified by flash chromatography using a silica gel column and a a mixture of petroleum ether and ethyl acetate (7:3) as eluent (R.f.=0.49). The product could be isolated in 38.6 mg (63% yield). Spectral data for **4** is in accordance with the literature[1] Spectral data for **6** is in accordance with the literature.[4]

7.3 Novel synthesis of *β*-seleno and *β*-sulfido carbonyl compounds

The next protocol for the synthesis of the ArSe-Bpin and ArS-Bpin reagents was developed by Westcott's group.

7.3.1 Synthesis and characterization of 4,4,5,5-tetramethyl-2-(phenylselanyl)-1,3,2-dioxaborolane (PhSe-Bpin)

To a toluene (10 mL) solution of benzeneselenol (2.22 g, 14.13 mmol) and pinacolborane (1.85 g, 14.45 mmol) was added a $RhCl(PPh_3)_3$ (3 mg, 0.0035 mmol, 0.02 mol%) as a solid. The reaction was allowed to proceed for 18 h,

at which point solvent was removed under vacuum to give an off-white solid. The solid was dissolved in hexane (4 mL) and stored at -30 °C. The resulting precipitate was collected by suction filtration to afford 1 as an off-white solid. Yield: 3.55 g (89%); mp 55-57 °C.

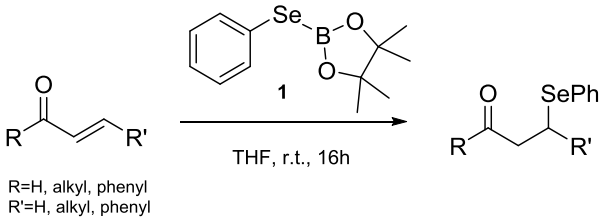
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (m, 2H, Ar), 7.25-7.20 (ov m, 3H, Ar), 1.32 (s, 12H, pin).

^{11}B NMR (128 MHz, $CDCl_3$) δ (ppm): 32.8 (br).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 134.5, 129.0, 126.8, 124.9, 85.7, 24.7.

Anal. Calcd. for $C_{12}H_{17}BO_2Se$ (283.03): C, 50.92; H, 6.05. Found: C, 51.23; H, 6.11.

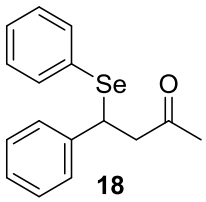
7.3.2 General procedures for the *β*-selenation of *α,β*-unsaturated ketones and aldehydes



PhSe-Bpin (30 mg, 0.11 mmol, 1.1 eq.) was weighted and transferred into an oven-dried schlenk tube inside the glovebox. The corresponding substrate (0.10 mmol) was introduced in the Schlenk tube under argon and dry THF (2 mL) was added. The mixture was stirred for 16 hours at room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at r.t, and analyzed by ^{1}H NMR. Conversion was determined by correlation of the integrals of the protons of the product and the substrate. The product *β*-(phenylseleno) substituted ketone was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and ethyl acetate adequate for each case.

7.3.3 Characterization of *β*-(phenylseleno) substituted ketones and aldehydes

4-phenyl-4-phenylseleno-2-butanone (18)



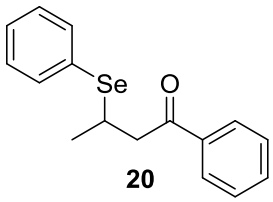
18

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 – 7.34 (m, 2H), 7.32 – 7.11 (m, 8H), 4.80 – 4.76 (dd, *J*=8.6, 6.4 Hz, 1H), 3.26 – 3.20 (dd, *J*=17.1, 8.6 Hz, 1H), 3.12 – 3.04 (dd, *J*=17.1, 6.4 Hz, 1H), 2.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 206.3, 141.9, 136.2, 129.4, 129.3, 128.9, 128.6, 128.0, 127.6, 50.0, 42.1, 31.0.

m/z: 304.04 (100.0%), 302.04 (50.2%), 306.04 (19.1%), 300.04 (18.7%), 301.04 (18.5%), 305.04 (17.4%), 303.04 (8.4%), 307.04 (3.1%), 298.04 (1.8%).

1-phenyl-3-phenylseleno-1-butanone (20)



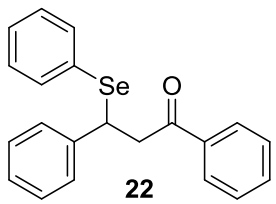
20

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 – 7.83 (m, 2H), 7.60 – 7.54 (m, 3H), 7.49 – 7.37 (m, 2H), 7.30 – 7.25 (m, 3H), 3.95 – 3.86 (m, 1H), 3.41 – 3.36 (dd, *J*=16.8, 5.0 Hz, 1H), 3.12 – 3.04 (dd, *J*=16.8, 10.1Hz, 1H), 2.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.4, 137.0, 135.5, 133.4, 131.8, 129.3, 128.8, 128.3, 128.0, 46.6, 33.7, 22.2

m/z: 304.04 (100.0%), 302.04 (50.2%), 306.04 (19.1%), 300.04 (18.7%), 301.04 (18.5%), 305.04 (17.4%), 303.04 (8.4%), 307.04 (3.1%), 298.04 (1.8%).

1,3-bisphenyl-3-phenylseleno-1-propanone (22)



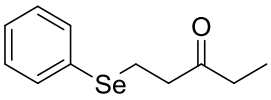
22

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 – 7.74 (m, 2H), 7.53 – 7.41 (m, 1H), 7.41 – 7.29 (m, 4H), 7.26 – 7.04 (m, 8H), 4.94 – 4.90 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.75 (dd, *J* = 17.3, 8.6 Hz, 1H), 3.56 (dd, *J* = 17.3, 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.5, 141.7, 136.8, 135.9, 133.4, 129.2, 129.2, 128.8, 128.6, 128.3, 128.2, 127.8, 127.3, 44.9, 42.2

m/z: 366.05 (100.0%), 364.05 (47.9%), 367.06 (23.1%), 363.06 (19.7%), 362.05 (18.9%), 368.05 (17.6%), 365.06 (11.4%), 369.06 (4.3%), 364.06 (4.0%), 368.06 (2.7%), 360.06 (1.8%), 366.06 (1.3%).

5-phenylseleno-3-pentanone (24)



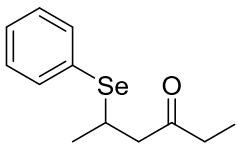
24

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 – 7.43 (m, 2H), 7.31 – 7.17 (m, 3H), 3.08 (t, *J* = 7.5 Hz, 2H), 2.89 – 2.77 (t, *J* = 7.5 Hz, 2H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 210.0, 135.0, 129.9, 129.3, 127.3, 43.0, 36.3, 20.8, 7.9.

m/z: 242.02 (100.0%), 240.02 (47.9%), 238.02 (18.9%), 244.02 (17.6%), 239.02 (15.4%), 243.02 (11.9%), 241.03 (5.9%), 239.03 (2.3%), 245.02 (2.1%), 240.03 (2.0%), 236.03 (1.8%).

5-phenylseleno-3-hexanone (26)



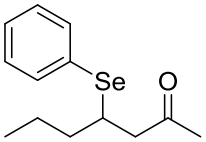
26

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 – 7.51 (m, 2H), 7.35 – 7.21 (m, 3H), 3.81 – 3.65 (m, 1H), 2.80 (dd, *J* = 16.9, 5.7 Hz, 1H), 2.66 (dd, *J* = 16.9, 8.4 Hz, 1H), 2.47 – 2.29 (q, *J* = 7.3 Hz, 2H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.7, 135.3, 129.2, 128.8, 128.0, 50.2, 36.8, 33.3, 22.2, 7.8.

m/z: 256.04 (100.0%), 254.04 (49.7%), 252.04 (18.8%), 258.04 (18.5%), 253.04 (17.8%), 257.04 (13.1%), 255.04 (6.3%), 259.04 (2.3%), 250.04 (1.8%).

4-phenylseleno-2-heptanone (28)



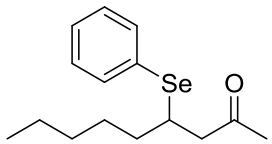
28

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 – 7.48 (m, 2H), 7.28 (m, 3H), 3.67 – 3.49 (m, 1H), 2.78 (dd, *J* = 17.3, 6.9, 1H), 2.75 (dd, *J* = 17.3, 6.0, 1H), 2.11 (s, 3H), 1.66 – 1.33 (m, 4H), 0.96 – 0.81 (t, *J* = 7.3, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.2, 135.5, 129.2, 128.7, 127.9, 50.2, 39.4, 37.9, 30.7, 21.2, 13.9.

m/z: 270.05 (100.0%), 268.05 (47.9%), 266.05 (18.9%), 267.06 (18.1%), 272.05 (17.6%), 271.06 (14.3%), 269.06 (7.0%), 273.06 (2.6%), 268.06 (2.4%), 264.06 (1.8%), 272.06 (1.2%).

4-phenylseleno-2-nonanone (30)



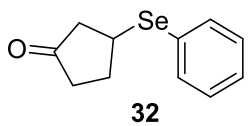
30

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 – 7.50 (m, 2H), 7.34 – 7.21 (m, 3H), 3.64 – 3.50 (m, 1H), 2.78 (dd, *J* = 17.3, 6.9 Hz, 1H), 2.69 (dd, *J* = 17.3, 6.3 Hz, 1H), 2.11 (s, 3H), 1.66 – 1.56 (m, 2H), 1.56 – 1.34 (m, 2H), 1.34 – 1.18 (m, 4H), 0.94 – 0.78 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.2, 135.5, 129.2, 128.7, 127.9, 50.2, 39.7, 35.7, 31.6, 30.7, 27.7, 22.7, 14.2.

m/z: 298.08 (100.0%), 296.08 (47.9%), 294.09 (18.9%), 295.09 (18.5%), 300.08 (17.6%), 299.09 (16.6%), 297.09 (8.1%), 301.09 (3.0%), 296.09 (2.8%), 292.09 (1.8%), 300.09 (1.5%).

3-phenylseleno-1-cyclopentanone (32)



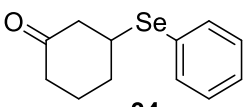
32

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 – 7.48 (m, 2H), 7.36 – 7.19 (m, 3H), 3.90 (m, 1H), 2.74 – 2.57 (dd, *J*= 18.8, 7.6 Hz, 1H), 2.51 – 2.14 (m, 4H), 2.14 – 1.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 217.0, 135.2, 131.7, 129.4, 128.5, 128.3, 45.9, 37.6, 37.5, 30.3.

m/z: 240.01 (100.0%), 238.01 (49.7%), 236.01 (18.8%), 242.01 (18.4%), 237.01 (17.6%), 241.01 (12.0%), 239.01 (5.8%), 243.01 (2.1%), 234.01 (1.8%)

3-phenylseleno-1-cyclohexanone (34)



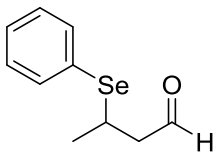
34

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 – 7.51 (m, 2H), 7.29 (m, 3H), 3.54 – 3.39 (m, 1H), 2.84 – 2.70 (dd, *J* = 14.2, 8.9 Hz, 1H), 2.46 (dd, *J* = 14.2, 11.2 Hz, 1H), 2.41 – 2.05 (m, 4H), 1.90 – 1.61 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.1, 135.9, 129.4, 128.4, 127.6, 48.9, 41.1, 40.4, 32.3, 25.4.

m/z: 254.02 (100.0%), 252.02 (47.9%), 250.02 (18.9%), 256.02 (17.6%), 251.02 (15.4%), 255.02 (13.0%), 253.03 (6.5%), 251.03 (2.5%), 257.02 (2.3%), 252.03 (2.2%), 248.03 (1.8%), 256.03 (1.0%).

3-phenylseleno-1-butanal (38)



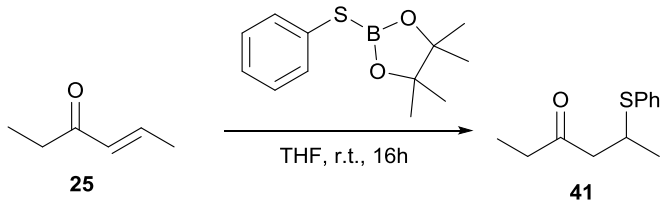
38

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.72 (t, *J* = 1.7 Hz, 1H), 7.64 – 7.49 (m, 2H), 7.38 – 7.28 (m, 3H), 3.79 – 3.62 (m, 1H), 2.75 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.60 (dd, *J* = 17.6, 8.7 Hz, 1H), 1.52 – 1.42 (d, *J* = 3.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 200.9, 135.8, 129.3, 128.3, 128.0, 51.1, 31.9, 22.3.

m/z: 240.01 (100.0%), 238.01 (49.7%), 236.01 (18.8%), 242.01 (18.4%), 237.01 (17.6%), 241.01 (12.0%), 239.01 (5.8%), 243.01 (2.1%), 234.01 (1.8%).

7.3.4 General procedure for the synthesis of 5-phenylsulfanyl-hexan-3-one (41)

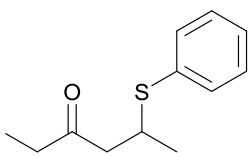


25 41

PhS-Bpin (0.11 mmol, 1.1 eq.) was weighted and transferred into an oven-dried schlenk tube inside the glovebox. 4-Hexen-3-one (0.10 mmol) was introduced in the Schlenk tube under argon and dry THF (2 mL) was added. The mixture was stirred for 16 hours at room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at r.t, and analyzed by ^{1}H NMR. Conversion was determined by correlation of the integrals of the protons of the product and the substrate. The product *β*-(phenylsulfanyl) substituted ketone was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and ethyl acetate (1:1).

7.3.5 Characterization of 5-phenylsulfanyl-hexan-3-one (41)

5-phenylsulfanyl-hexan-3-one (41)



41

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 – 7.35 (m, 2H), 7.35 – 7.16 (m, 3H), 3.81 – 3.62 (m, 1H), 2.72 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.54 (dd, *J* = 16.8, 8.5 Hz, 1H), 2.46 – 2.29 (q, *J* = 8.5 Hz, 2H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.03 (t, *J* = 8.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.2, 134.4, 132.4, 129.1, 127.4, 49.6, 38.9, 37.3, 21.7, 8.3.

m/z: 208.09 (100.0%), 209.10 (13.2%), 210.09 (4.6%), 210.10 (1.0%).

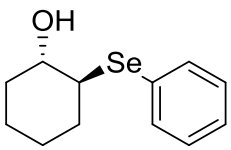
7.4 An experimental approach to the metal-free selenolysis and thiolysis of epoxides

7.4.1 General procedures for the selenolysis of epoxides

The reagent PhSe-Bpin (0.60 mmol, 2 eq.) was weighted and transferred into an oven-dried schlenk tube inside the glovebox. The substrate (0.30 mmol) was introduced in the Schlenk tube under argon and dry THF (3 mL) was added. The mixture was stirred for 16 hours at room temperature. An aliquot of 0.1 mL was taken from the solution and gently concentrated on a rotary evaporator at rt, and analyzed by ^{1}H NMR. Conversion was determined on some cases by correlation of the integrals of the protons of the product and the substrate. The product *β*-hydroxy selenide was purified by flash chromatography using a silica gel column, and the suitable mixture of petroleum ether and ethyl acetate (9:1).

7.4.2 Characterization of the *β*-hydroxy selenides

***anti* 2-(Phenylselanyl)cyclohexanol (71)**

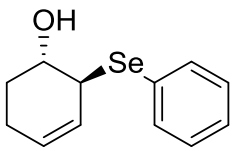


71

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (dd, *J* = 6.6, 3.2, 2H), 7.27 (m, 3H), 3.30 (m, 1H), 2.98 (br s, OH), 2.79 (m, 1H), 2.13 (m, 2H), 1.71 (m, 1H), 1.58 (m, 1H), 1.48 – 1.04 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.3, 129.2, 128.4, 126.8, 72.5, 53.8, 34.1, 33.6, 27.1, 24.7.

***anti* 2-(Phenylselanyl)cyclohex-3-en-1-ol (72)**

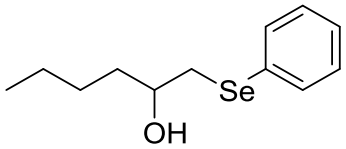


72

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (m, 2H), 7.28 (m, 3H), 5.83 (m, 1H), 5.72 (m, 1H), 3.88 (ddd, *J* = 8.6, 5.9, 2.7 Hz, 1H), 3.71 (m, 1H), 2.26 – 2.02 (m, 3H), 1.69 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.1, 129.5, 129.4, 128.2, 126.7, 70.4, 48.8, 27.5, 22.9.

1-(Phenylselanyl)hexan-2-ol (75)

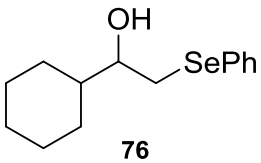


75

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (m, 2H), 7.26 (m, 3H), 3.65 (m, 1H), 3.15 (dd, *J*=12.8, 3.2 Hz, 1H), 2.86 (dd, *J*=12.8, 8.4 Hz, 1H), 2.36 (br s, OH), 1.50 (m, 2H), 1.46 – 1.16 (m, 4H), 0.88 (t, *J*=6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.3, 129.6, 129.5, 127.5, 70.1, 37.6, 36.6, 28.3, 22.9, 14.3.

1-Cyclohexyl-2-(phenylselanyl)ethan-1-ol (76)

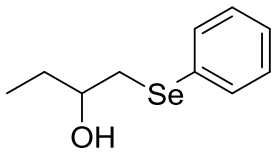


76

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (d, 2H), 7.26 (m, 3H), 3.41 (m, 1H), 3.20 (dd, *J*=12.7, 3.0 Hz, 1H), 2.91 (dd, *J*=12.7, 9.4 Hz, 1H), 2.36 (br s, OH), 1.89-1.82 (m, 1H), 1.78 – 1. 61 (m, 4H), 1.50 – 1.40 (m, 1H), 1.27-0.96 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.2, 129.4, 127.4, 74.1, 43.4, 35.4, 29.4, 28.5, 26.6, 26.4, 26.3.

1-(Phenylselanyl)butan-2-ol (77)

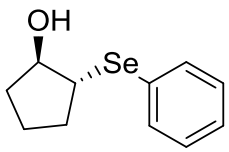


77

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (m, 2H), 7.27 (m, 3H), 3.61 (m, 1H), 3.15 (dd, *J*=12.8, 3.5 Hz, 1H), 2.88 (dd, *J*=12.8, 8.7 Hz, 1H), 2.38 (br s, OH), 1.57 (m, 2H), 0.94 (t, *J*=7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.2, 129.6, 129.4, 127.5, 71.3, 37.1, 29.7, 10.3.

2-(Phenylselanyl)cyclopentan-1-ol (78)



78

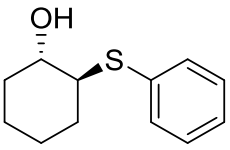
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.57 (m, 2H), 7.28 (m, 3H), 4.17 (m, 1H), 3.42 (m, 1H), 2.26 (m, 1H), 2.07 (m, 1H), 1.85–1.55 (m, 4H).

7.4.3 General procedures for the thiolysis of epoxides

The reagent PhS-Bpin (0.60 mmol, 2 eq.) was weighted and transferred into an oven-dried schlenk tube inside the glovebox. The substrate (0.30 mmol) was introduced in the Schlenk tube under argon and dry THF (3 mL) was added. The mixture was stirred for 16 hours at room temperature. An aliquot of 0.1 mL was taken from the solution and gently concentrated on a rotary evaporator at rt, and analyzed by ^{1}H NMR. Conversion was determined on some cases by correlation of the integrals of the protons of the product and the substrate. The product *β*-hydroxy sulfide was purified by flash chromatography using a silica gel column, and the suitable mixture of petroleum ether and ethyl acetate (9:1).

7.4.4 Characterization of the *β*-hydroxy sulfides

***anti* 2-(phenylthio)cyclohexan-1-ol (79)**

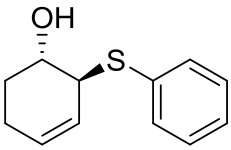


79

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.44 (m, 2H), 7.26 (m, 3H), 3.29 (dt, *J*= 10.0, 4.5 Hz, 1H), 2.94 (br s, OH), 2.75 (m, 1H), 2.08 (m, 2H), 1.66 (m, 2H), 1.34-1.16 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 134.1, 129.2, 128.1, 72.3, 56.8, 34.1, 33.0, 26.5, 24.6.

***anti* 2-(Phenylthio)cyclohex-3-en-1-ol (80)**

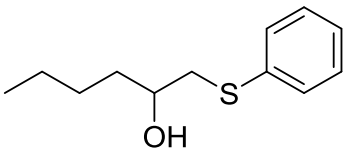


80

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (m, 2H), 7.29 (m, 3H), 5.85 – 5.66 (m, 2H), 3.78 (ddd, *J* = 9.2, 6.6, 2.8 Hz, 1H), 3.62 (dt, *J* = 6.6, 2.2 Hz, 1H), 2.31 – 1.96 (m, 3H), 1.67 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 132.6, 129.8, 129.2, 127.7, 126.1, 69.7, 52.7, 27.9, 23.3.

1-(Phenylthio)hexan-2-ol (81)

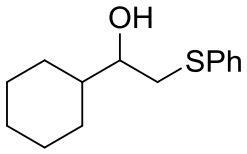


81

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (m, 2H), 7.30 (m, 2H), 7.20 (m, 1H), 3.66 (m, 1H), 3.16 (dd, *J* = 13.7, 3.3 Hz, 1H), 2.84 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.54 (m, 3H), 1.28 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 130.3, 129.3, 127.7, 126.8, 69.6, 42.5, 36.1, 28.1, 22.9, 14.3.

1-Cyclohexyl-2-(phenylthio)ethan-1-ol (82)

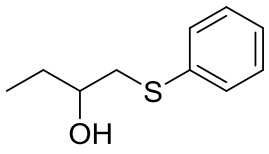


82

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 1H), 7.29 (m, 1H), 7.21 (m, 1H), 3.43 (m, 1H), 3.23 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.86 (dd, *J* = 13.6, 9.4 Hz, 1H), 1.89 (m, 1H), 1.70 (m, 4H), 1.44 (m, 1H), 1.31 – 0.97 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.3, 129.9, 129.0, 126.5, 73.2, 42.7, 39.9, 29.0, 28.2, 26.4, 26.1, 26.0.

1-(Phenylthio)butan-2-ol (83)



83

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (m, 2H), 7.26 (m, 2H), 7.19 (m, 1H), 3.57 (m, 1H), 3.13 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.81 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.53 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 135.4, 130.2, 129.2, 126.7, 70.7, 42.0, 29.1, 10.1.

7.5 References

[1] S. Crotti, F. Bertolini, F. Macchia, M. Pineschi, *Org. Lett.,* **2009**, *11*, 3762.

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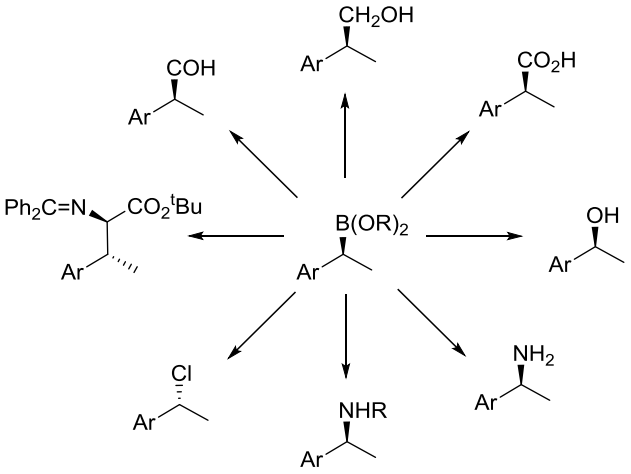
UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

8. Summary

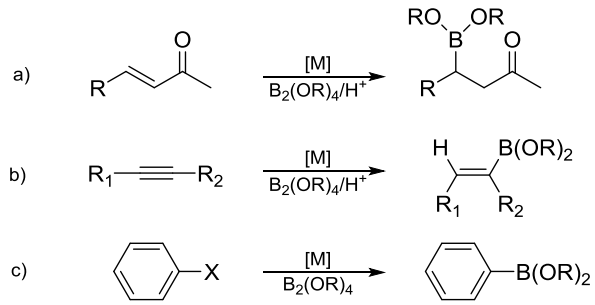
UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

Nowadays, organoboranes are relevant compounds as they can be used as intermediates in the synthesis of many functionalized molecules.[1] Moreover, organoboron reagents have potential applications in biochemistry and biomedical sciences due to their biological activity.[2] Organoboranes can be easily prepared through well established protocols.[3] Particularly, the catalytic C-B bond formation is interesting because it serves as a platform for further transformations with total control of the chemo-, regio- and stereoselectivity of the product formation (Scheme 1.1).[4]



Scheme 8.1. Some of the typical transformations of the C-B bond.

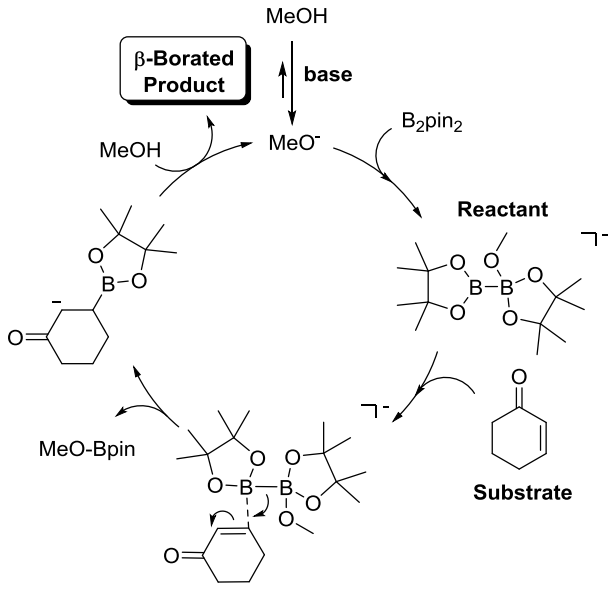
Diborons are the most used reagents used to introduce boron moieties into unsaturated substrates. However, they present different behavior depending on the reaction conditions and the nature of the substrate they react with. Thus, other less atomic economical reactions such us *β*-boration, hydroboration and borylation of unsaturated compounds can happen (Scheme 8.2).



Scheme 8.2. Alternative reactions of diboranes: *β*-boration (a), hydroboration (b) and borylation (c).

It is well known that the B-B bond is rather strong (104 kcal·mol^{-1})[5] and this might be the cause of the unsuccessful direct addition of diboron reagents to C-C multiple bonds.[6] Therefore, tetralkoxydiborons need to be activated to react with unsaturated substrates. The most extended method to activate diboron reagents is mainly performed by transition metal catalysts *via* homolytic oxidative addition or *via* σ-bond metathesis (heterolytic cleavage of the B-B bond).

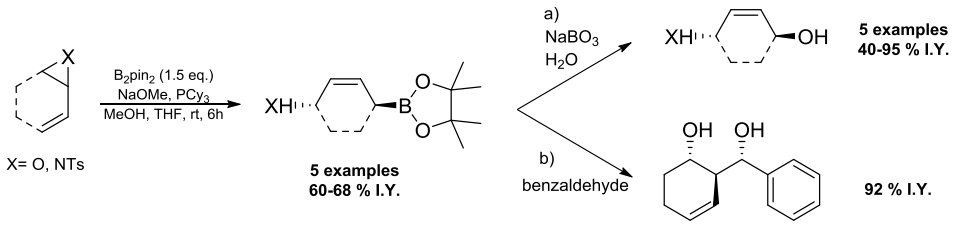
On the other hand, the diboron reagents have been reported to be also activated without the need of a transition metal. Intermolecular activation of symmetrical diborons such as B_2pin_2 can create a significant nucleophilic boryl synthon, which in the absence of any transition metal complexes can efficiently be transferred to the C_β of *α,β*-unsaturated carbonyl compounds. The so-called "pull-push effect" of the B is understood as the quaternization of one B atom of the diboron forming an activated adduct which subsequently releases a boryl unit with enhanced nucleophilicity. During this process, the sp^2 boron of the [B_2pin_2·MeO^-] adduct gained a pronounced nucleophilic character and attacked the electron deficient olefins (Scheme 8.3).



Scheme 8.3. Proposed catalytic cycle for the methoxide-mediated metal-free *β*-boration of *α,β*-unsaturated compounds with B_2pin_2.

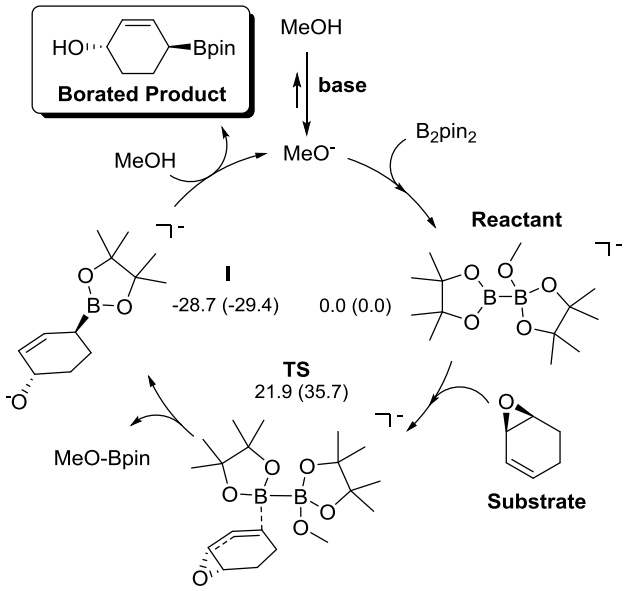
In this line, we found interesting to extend our group's metal-free methodology to the borylative ring opening of vinyl epoxides and aziridines since all the previously reported cases were catalyzed by metals such as palladium,[7] nickel[7a, 8] or copper.[9]

The *in situ* formed $[B_2pin_2 \cdot OMe]^-$ adduct successfully reacted with vinyl epoxides and aziridines. The SN_2' exclusively took place giving the alkylboronate products in *anti*. Up to 5 substrates were borylated using this methodology and were isolated in up to 68% yield. Further functionalization of the allylboronate products *via* oxidation or reactivity with benzaldehyde allowed us to confirm the stereostructures (Scheme 8.4).



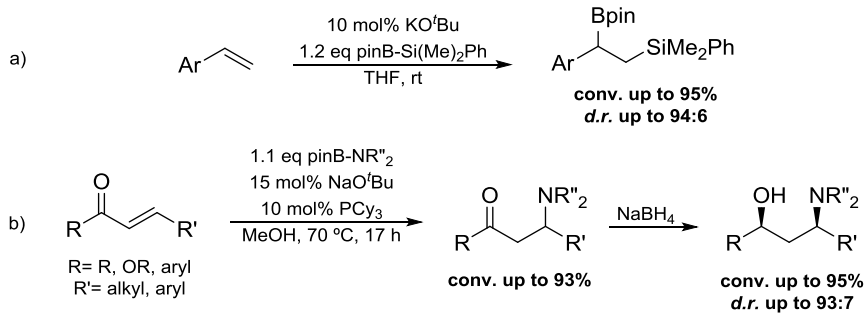
Scheme 8.4. Metal-free borylative ring opening of vinyl epoxides and aziridines.

From a theoretical point of view, we proposed a plausible mechanism for this reaction. The mechanism is in accordance with our experimental results and helps to understand the role of each reagent in the reaction (Scheme 8.5).



Scheme 8.5. Proposed reaction pathway for the borylative ring-opening of vinyl epoxides and vinyl aziridines with B_2pin_2. Electronic energy and Gibbs free energy (in parenthesis) computed at the M06-2X level relative to $[B_2pin_2 \cdot OMe]^-$ adduct plus 3,4-epoxy-1-cyclohexene (**1**) as a model substrate. All values are in kcal·mol^{-1}.

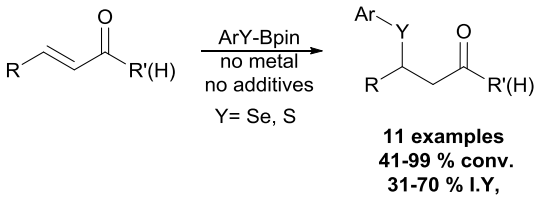
On the other hand, quaternization of one boron atom in species containing B-E bonds (E= elements from group 14) induces the heterolytic cleavage of these stable bonds. The so-called *pull-push* effect of B has also been studied with silanoboranes and aminoboranes, achieving respectively the silaboration[10] and aminoboration[11] of activated alkenes and alkynes (Scheme 8.6).



Scheme 8.6. Metal-free a) silaboration and b) aminoboration of activated alkenes.

In this context, we initiated collaboration with Prof. Westcott's group to explore the reactivity of a family of novel B-Y species (Y= Se, S)[12] when reacting with electrophilic substrates.

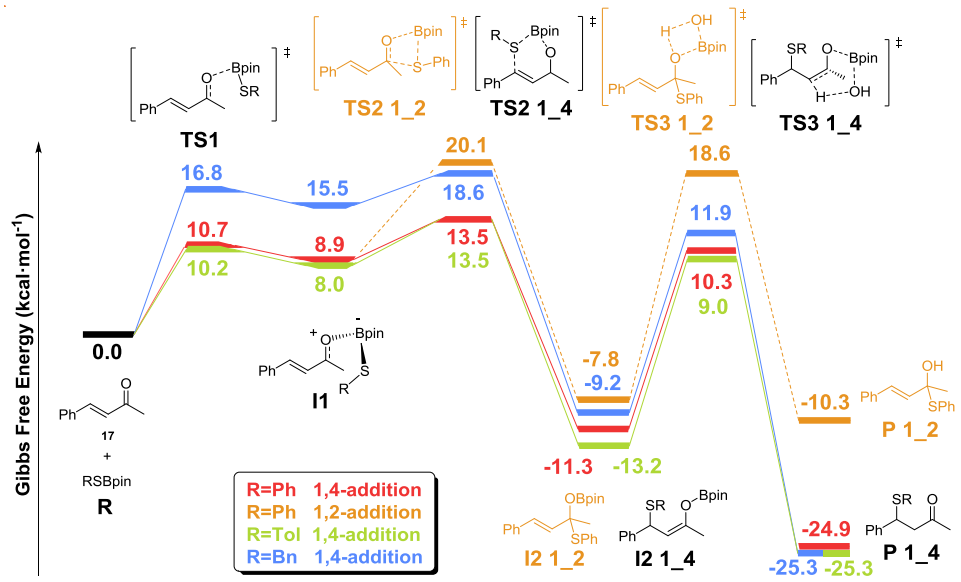
We first studied the activation of the Se-B reagent in the presence of vinyl ketones and aldehydes. Remarkably, exclusively the *β*-seleno and *β*-sulfido products were obtained in a face to face reaction. The carbonylic oxygen atom of the substrate seems able to activate the reagent and thus the reaction takes place without the need of expensive metal species or additives (Scheme 8.7).



Scheme 8.7. Metal-free *β*-selenation of vinyl ketones and aldehydes.

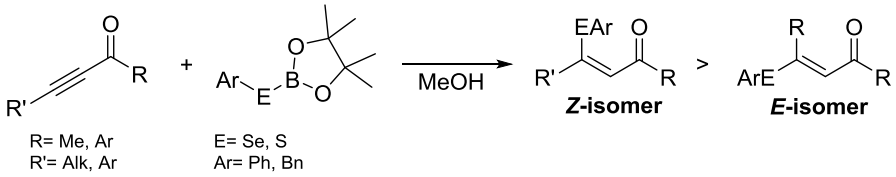
Moreover, DFT studies facilitated the understanding of the reaction outcome and helped to predict the reactivity of the analogous sulphur and oxygen analogous through the calculation of nucleophilicity indexes. Interestingly we found out that the B-Se reagent was the most nucleophilic reagent, nearly followed by B-S. The B-O analogous appeared to be the least nucleophile. We corroborated that the sulphur analogous presents a very similar reactivity and we proved this with an experimental example of direct reaction between PhS-Bpin and 4-hexen-3-one (**25**).

We next proposed a plausible mechanism of the reaction for all the RY-Bpin (Y= Se, S, O) reagents and as expected, the oxygen reagent appeared to be unreactive due to the high activation energy values and instability of the reaction intermediates. We clearly observed that the BnS-Bpin was the less active among the B-S reagents, whilst PhS-Bpin and TolS-Bpin appeared to be very similar (Scheme 8.8). In all cases the 1,2-addition was totally disfavored, which is in agreement with the experimental exclusive observation of the *β*-selenated and *β*-thionated products.



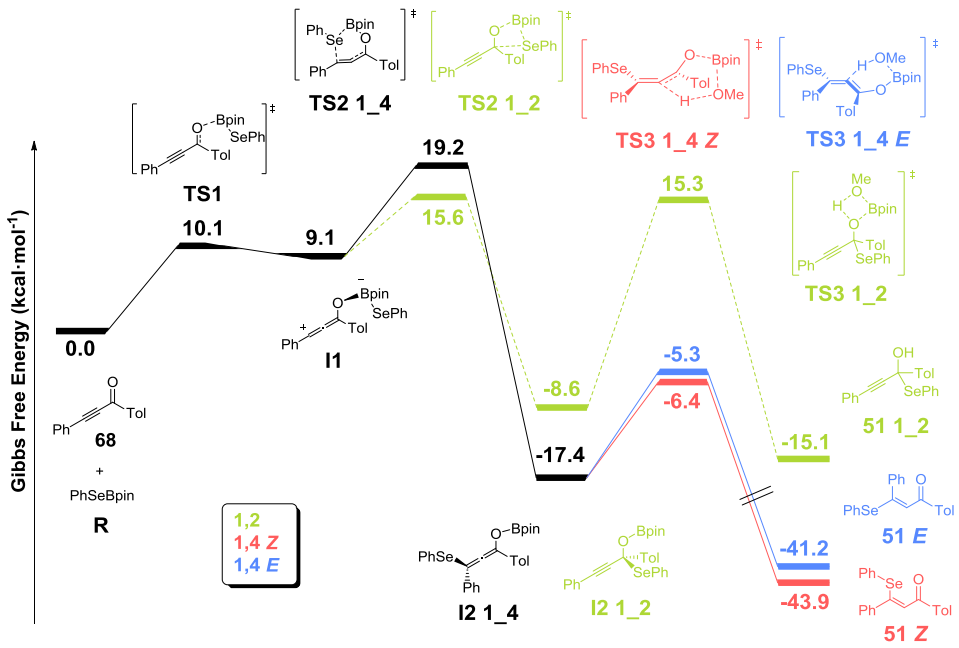
Scheme 8.8. Relative Gibbs Free Energies for the reaction pathway of the 1,2- and 1,4-addition of the RS-Bpin reagents to the substrate 4-phenyl-3-buten-2-one (**17**). All energies are in kcal·mol^{-1}.

Our next interest was to promote the same reaction for the propargylic ketones. My co-worker M. Garcia was able to successfully prepare a number of vinyl sulfides and selenides using the same simple metal-free methodology with good to excellent conversion and isolated yield values. The reaction appeared to be selective towards the obtaining of the *Z* isomers (Scheme 8.9).



Scheme 8.9. Synthesis of vinyl selenides and vinyl sulfides throughout chalcogenoborates.

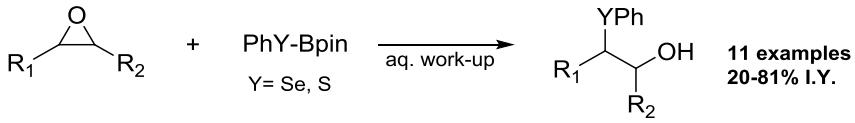
The reaction was next studied by means of DFT and we proposed a plausible mechanism that justifies the only observation of the 1,4-addition products. Also, the *Z* isomer seemed to be the most favored (Scheme 8.10).



Scheme 8.10. Relative Gibbs free energies for the reaction pathway of the 1,2- and 1,4-addition of the PhSe-Bpin reagent to the model substrate 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**68**). All energies are in kcal·mol^{-1}.

The last project of this thesis consisted in the reaction of PhSe-Bpin and PhS-Bpin reagents with epoxides. Our aim was to afford *β*-hydroxy selenides and sulfides following the same procedure that we previously utilized. We expected that the nucleophilic PhSe$^-$ or PhS$^-$ moiety would attack the epoxide to generate the desired products.

Again, simply by mixing both the reagent and the substrate in a solvent, the formation of the ring opening products could be observed. Nonetheless, conversion values were not totally reliable and for this reason we measured all isolated yields. Only 6 substrates could be successfully selenated and five thionated since we found our limitation on the substrate scope after have no conversion for 12 tested substrates (Scheme 8.11). The reaction was selective towards the *anti* products and the nucleophilic moiety attacked in all cases the terminal position of the epoxides.



Scheme 8.11. Reaction scheme of the reaction of PhSe-Bpin and PhS-Bpin with epoxides.

DFT studies revealed that a first coordination of the PhSe-Bpin reagent to the substrate might occur *via* B-O interaction. A transition state for the ring opening was found, although the nucleophilic attack of the released $PhSe^-$ moiety to the electrophilic carbon appeared to be barrierless. In addition, the disposition of the O, B, Se and C atoms in the space seems to lead to the *syn* attack and therefore to the *cis* product. Since the only observed product was the *trans* isomer, we suggested that once the PhSe- nucleophile is released, it might attack another substrate molecule by the lower and less-hindered face.

References

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Appendix

UNIVERSITAT ROVIRA I VIRGILI
THEORETICAL AND EXPERIMENTAL UNDERSTANDING OF THE PULL-PUSH EFFECT ON THE SYNTHESIS OF ORGANO-BORANES, SULFIDES AND SELENIDES
Xavier Sanz López

Publications

"Ynones merge activation/conjugate addition of chalcogenoborates ArE-Bpin (E= Se, S)"

Authors: M. G. Civit, X. Sanz, C. M. Vogels, C. Bo, S. A. Westcott, E. Fernández.

Journal: *Adv. Synth. Catal.*, **2015** (Accepted manuscript)

"Organocatalytic functionalisation through boron chemistry."

Authors: G. Palau-Lluch, X. Sanz, E. LaCascia, M. G. Civit, N. Miralles, A. B. Cuenca, E. Fernández.

Journal: *Pure Appl. Chem.*, **2015**, *87*, 181.

"Thioboration of α,β-unsaturated ketones and aldehydes toward the synthesis of β-sulfido carbonyl compounds."

Authors: M. G. Civit, X. Sanz, C. M. Vogels, J. D. Webb, S. J. Geier, A. Decken, C. Bo, S. A. Westcott, E. Fernández.

Journal: *J.Org. Chem.*, **2015**, *80*, 2148.

"Asymmetric metal free β-boration of α,β-unsaturated imines assisted by (S)-MeBoPhoz."

Authors: E. LaCascia, X. Sanz, C. Bo, A. Whiting, E. Fernández.

Journal: Org. Biomol. Chem., **2014**, *13*, 1328.

"Face to face activation of a phenylselenium borane with α,β-unsaturated carbonyl substrates: facile synthesis of C-Se bonds."

Authors: X. Sanz, C. M. Vogels, A. Decken, C. Bo, S. A. Westcott, E. Fernández.

Journal: *Chem. Commun.*, **2014**, *50*, 8420.

"Metal-free borylative ring-opening of vinyl epoxides and aziridines."

Authors: X. Sanz, G. M. Lee, C. Pubill-Ulldemolins, A. Bonet, H. Gulyás, S. A. Westcott, C. Bo, E. Fernández.

Journal: *Org. Biomol. Chem.*, **2013**, *11,* 7004.

Conference contributions

OMCOS 18 28/06/2015 - 02/07/2015

Sitges, Barcelona, Spain

Poster: "Direct interaction of pinB-SePh and pinB-SPh with epoxides"

Authors: Xavier Sanz, Christopher M. Vogels, Carles Bo, Stephen A. Westcott, Elena Fernández.

Poster: "Ynones activate ArS-Bpin and PhSe-Bpin to synthesize *α*-keto vinyl selenides and sulfides"

Authors: Marc G. Civit, Xavier Sanz, Christopher M. Vogels, Carles Bo, Stephen A. Westcott, Elena Fernández.

XXXII GEQO 17/09/2014 - 19/09/2014

Tarragona, Spain

Poster: "Face to face activation of a phenylselenium borane with *α,β*-unsaturated carbonyl substrates: Facile synthesis of C-Se bonds."

Authors: Xavier Sanz, Christopher M. Vogels, Carles Bo, Stephen A. Westcott, Elena Fernández.

XV IMEBORON 24/08/2014 - 28/08/2014

Prague, Czech Republic

Poster: "Face to face activation of a phenylselenium borane with *α,β*-unsaturated carbonyl substrates: Facile synthesis of C-Se bonds."

Authors: Xavier Sanz, Christopher M. Vogels, Carles Bo, Stephen A. Westcott, Elena Fernández.

ICIQ's 10th Anniversary Scientific Symposium 16/07/2014 - 18/07/2014

ICIQ, Tarragona, Spain

Poster: "Computational studies on the reactivity of small molecules: CO_2, epoxides, organoboranes…"

Authors: Fernando Castro-Gómez, Joan González-Fabra, Xavier Sanz, Elena Fernández, Carles Bo.

EUROBORON 6 08/09/2013 - 13/09/2013

Radziejowice, Poland

Poster and Flash Presentation: "Organocatalytic Borylative Ring Opening"

Authors: Xavier Sanz, Cristina Pubill-Ulldemolins, Henrik Gulyás, Carles Bo, Graham M. Lee, Stephen A. Westcott, Elena Fernández.

96th CSC 26/05/2013 - 30/05/2013

Québec, Canada

Oral Presentation: "Organocatalytic Borylative Ring Opening"

Authors: Xavier Sanz, Cristina Pubill-Ulldemolins, Henrik Gulyás, Carles Bo, Graham M. Lee, Stephen A. Westcott, Elena Fernández.

XVIII ISHC 09/07/2012 - 13/07/2012

Toulouse, France

Poster: "Organocatalytic Borylative Ring Opening"

Authors: Xavier Sanz, Henrik Gulyás, Carles Bo, Elena Fernández.

Research abroad

Project: "*Making inroads into thioboration chemistry*"

Center: Mount Allison University, NB, Canada.

Supervisor: Prof. Stephen Alan Westcott.

Period: June-August 2013.

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