AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL

Marc Garcia Civit

UNIVERSITAT ROVIRA i VIRGILI

Activation of B-interElement (E=S, Se) reagents towards selective C-S and C-Se bond formation

MARC GARCIA CIVIT
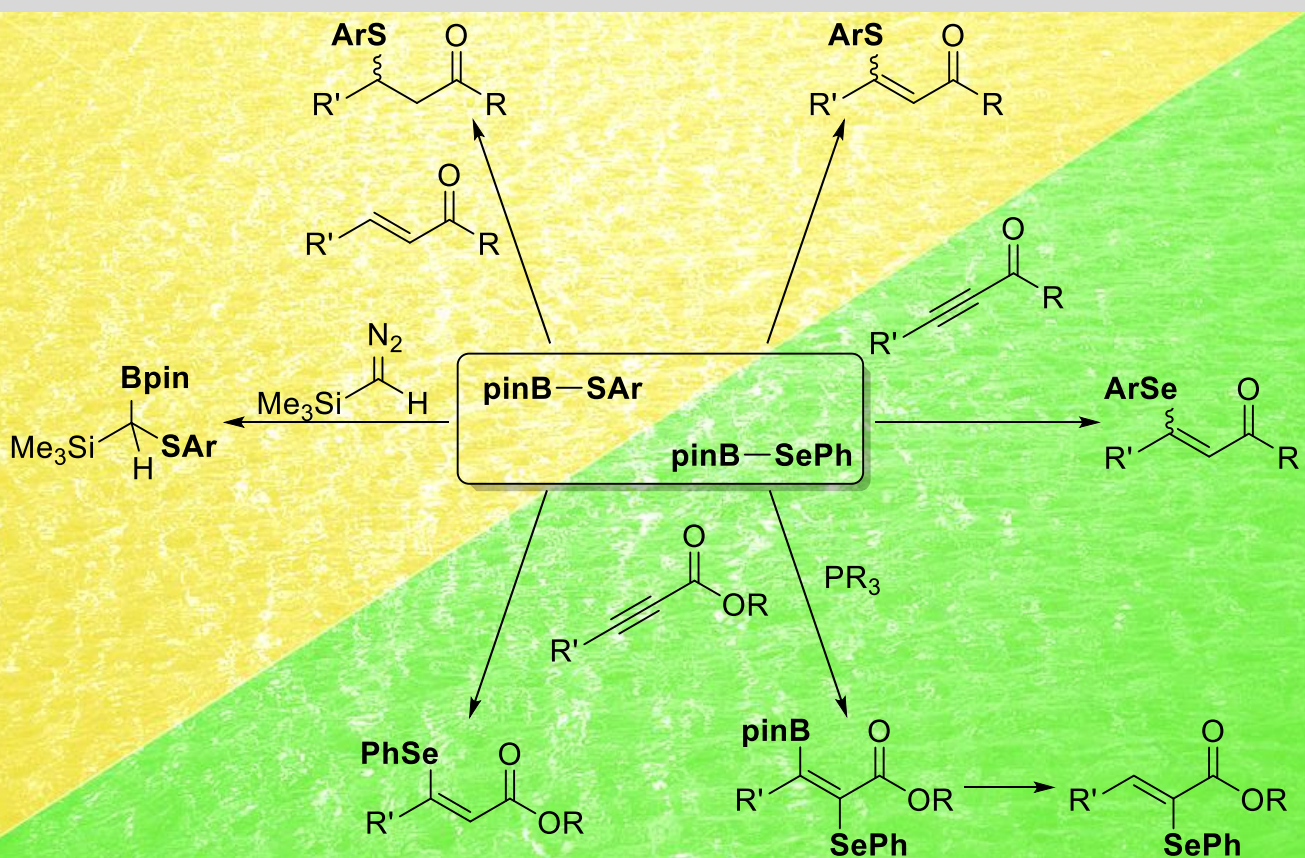
DOCTORAL THESIS
2017

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

Marc Garcia Civit

Activation of B-interElement (E=S, Se) reagents towards selective C-S and C-Se bond formation

DOCTORAL THESIS

Supervised by

Dr. Mª Elena Fernández Gutiérrez

UNIVERSITAT
ROVIRA i VIRGILI

Tarragona

2017

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

Departament de Química Física i Inorgànica
C/Marcel·lí Domingo s/n
Edifici N4
Campus Sescelades
43007 Tarragona
Tel. 977 55 81 37

UNIVERSITAT
ROVIRA i VIRGILI

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

FAIG CONSTAR que aquest treball, titulat "*Activation of B-interElement (E=S, Se) reagents towards selective C-S and C-Se bond formation*", que presenta el Sr. Marc Garcia Civit per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili.

Tarragona, 15 de maig de 2017

La directora de la tesi doctoral

Dra. Maria Elena Fernández Gutiérrez

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

Agraïments

En primer lloc vull agrair a la meva supervisora l'Elena per obrir-me les portes del grup del bor i per acompanyar-me i guiar-me al llarg del camí que he recorregut per l'apassionant món de la química durant aquest quatre anys. Encara recordo perfectament la conversa que vam tindre en aquell laboratori de química inorgànica a tercer quan em vas obrir els ulls i em vas animar a fer l'Erasmus. Mai et podré estar prou agraït per encoratjar-me a prendre la decisió que va marcar el meu inici en la investigació química i per tota la confiança que has depositat en mi des del començament. Elena et dono les gracies per tots els teus bons consells, totes les estones al teu despatx parlant sobre química, totes les oportunitats que m'has ofert per participar en congressos i per tots els *group meetings*, els formals i els informals, en els que amb el teu caràcter i manera de fer has aconseguit que els del bor siguem un GRUP tant dintre del laboratori com fora. El teu consell i suport ha sigut una peça clau durant totes les etapes de recerca que he viscut, moltes gràcies.

Seguidamente quiero darte las gracias a ti, Ana. Has sido un gran apoyo dentro del laboratorio con tus reflexiones y clases magistrales exprés que organizabas en un periquete utilizando la pantalla de la vitrina y un permanente que sacabas de algún bolsillo de tu bata. Gracias por estar siempre dispuesta a escuchar y a echar una mano cuando lo necesitaba. Con solo escuchar mis "Ana, saps que…" o un "buff…" ya sabias lo que necesitaba y allí estabas tú para ofrecérmelo de muy buen grado. Tu buen humor, las risas, las infinitas charlas que hemos tenido… han hecho que las largas columnas se hicieran cortas y las horas que hemos pasado entre las vitrinas del boro fueran siempre buenos momentos o anécdotas que recordar. Ha sido un gran placer compartir contigo mi viaje por la investigación química.

Thanks Steve Westcott and Chris Vogels for synthetizing, packaging and sending by plane the amazing and a bit smelly reagents (pinB-SPh, pinB-STol, pinB-SBn and pinB-SePh). I have been working with them for four years and I have never run out, thank you.

Durant tot aquest temps que he format part dels *Omichis* he compartit el viatge amb magnifiques persones a les que els hi tinc molt que agrair. Començaré pel companys del grup del bor amb els que he viscut totes les alegries que l'element número 5 de la taula periòdica m'ha donat. Núria vam començar a la vegada a descobrir el món del bor en aquell congrés a Polònia i fins ara, ha sigut tot un luxe poder recórrer aquest camí al costat d'una persona tant treballadora com ho ets tu. Amb tu Jordi he pogut compartir les insercions que, juntament amb l'Ana, ens ha fet gaudir de molt bons moments de treball en equip, moltes gràcies per la teva gran aportació al projecte. Albert ha sigut un plaer compartir els teus inicis pel laboratori, moltes gràcies per encomanar-me la teva energia i entusiasme per fer les coses. Gràcies a tots els veterans que tant m'heu ensenyat: Jesica Cid per acompanyar-me durant la meva iniciació al laboratori; Gerard has sigut un gran company del que he après molt; Xavi ha sigut tot un plaer treballar al teu costat amb els nostres sofres i selenis, han sigut molt enriquidores les teves aportacions teòriques i de mecanismes; Thierry gran company de vitrina amb el teu humor tant peculiar i les teves aportacions químiques, sempre et recordaré fent servir el Kugelrohr , Enrico tú también fuiste un gran compañero de vitrina y de habitación en muchos congresos con el que he reído hasta más no poder.

El laboratori 216 he tingut el plaer de compartir-lo amb gent magnifica que treballa amb nanopartícules i/o reactors. Eli, Jessica Llop, Itziar i Alberto la veu de l'experiència sempre disposada a ajudar; l'Aaron amb la seva música peculiar, el Fran i les seves nanos precipitant a la caixa seca, el Toni amb les seves columnes de com a mínim cinc quilos de producte, el Jordi

Creus i els seus viatges ICIQ/URV/Bcn/França on pares ara?, heu sigut uns grans companys i companyes. Nannette many thanks for all your chemistry advice and Myriam I hope you the best in your future as a chemist. Laura, sempre recordaré els bons moments viscuts al nostre seminari dels màsters i els teus trossets de paper pintat que catalitzen reaccions, moltes gràcies per totes les estones amenitzades amb riures i cançons. Una altra persona que utilitzava reactors i amb la que he compartit una part del meu trajecte ha sigut la Laia, un plaer.

Per últim però no menys important tenim a la fantàstica gent del 217 i tota les seves famílies de lligants: Jessica Margalef i Mercè grans químiques i millors persones, Fàtima també vas estar al seminari dels màsters i vas formar parts dels moments irrepetibles que allí va crear amb la Laura; Marc Magre al teu costat sempre serè el Marc petit; Carlota seguiré llegint la Vanguardia per no perdre la practica amb els jeroglífics, moltes gràcies per compartit tots els petits trucs químics que m'han ajudat en molts moments a fer columnes o preparar reaccions, Maria ens coneixem des de primer de carrera i els dos em arribat fins aquí, ha sigut un plaer recórrer aquesta cursa de fons i arribar fins aquí a la vegada; "Professor" Zahra it has been a pleasure to share lots of good moments, you have been always there to say "come on hombre!!" and convert bad things in better ones, thank you; Efrem i Joan gràcies pels bons moments parlant d'actualitat amb un diari al davant, us desitjo molts èxits.

Durant el transcurs d'aquesta tesi he tingut el plaer de rebre l'ajuda de magnifiques persones. Josep moltes gràcies per tot el material reparat i l'ajuda amb la gestió dels residus, Raquel moltes gràcies per estar sempre disposada a ajudar amb un gran somriure a la boca, les compres, els reactius, les fitxes de seguretat, la base de dades, la caixa seca, els dissolvents... sempre que t'he necessitat allí estaves i moltes moltes gràcies per preocupar-te en tot moment per la nostra seguretat.

Irene i Carme heu sigut de gran ajuda amb la cromatografia tant de gas com líquida, sempre disposades ha donar consell sobre quina serà la millor opció per analitzar les mostres, moltes gràcies per la vostra feina. Ramón i els RMN, moltes gràcies per ser-hi allí, durant els espectres de rutina com els més peculiars. Sempre disposat a recomanar un experiment nou per trobar la possible solució als peculiars casos que t'he plantejat. Tot i ser del bor pocs "su btune" hem hagut de fer, però d'altres experiments de RMN hem gaudit plegats amb el teu gran sentit de l'humor, moltes gràcies.

També vull agrair tot el suport i bons moments que m'ha brindat la família Tornavisera. Des de que vam deixar l'institut tots i totes heu sigut més que un grup de teatre, heu sigut uns molt bons amics i amigues amb els que he passat molt bones estones any rere any. Moltes gràcies als actors, al director, als tècnics, als veterans, a les noves incorporacions, als presents i als que han passat.

No em puc oblidar una part molt important del que sóc avui en dia, la gran família escolta i guia. Fa tres anys que sóc escolta i guia a l'AEiG Bisbe Borràs i només puc donar les gràcies a tots els caps pel bons moments que hem viscut junts i per ensenyar-me tantes coses que fins fa poc desconeixia. Maria moltes gràcies per ensenyar-me tant bé el que és ser escolta i guia, per les tardes plegats parlant de la vida i per ser un gran referent per mi dintre de l'escoltisme i el guiatge. Gemma des dels campaments conjunts fins ara estem recorrent un camí plegat que espero que continuï per molt temps, moltes gràcies per escoltar-me quan més ho he necessitat, per ser al meu costat i per riure i plorar a l'hora junts. Andrea que suerte tuve cuando nuestros caminos se cruzaron, siempre serás la primera persona a la que le firmé las prácticas como director y gracias por ser un gran apoyo y una fuente de risas inagotable durante todo este tiempo. Moltes gràcies als Companys escoltes i guies de la Demarcació de Tarragona, de MEG y a los scout de Griébal amb els que he compartit grans moments d'aprenentatge.

I per últim i més important moltes gràcies a tota la meva família. Mama i papa m'heu aguantat els meus canvis d'humor freqüents durant aquest temps i m'heu criat de la millor manera i mai us podré estar prou agraït per tot el que heu fet i feu per mi. Als meus germans Alex i Jordi sou el millor que em passarà a la vida i us vull al meu costat sempre com ho heu estat fins ara. Patri moltes gràcies per deixar-me parlar-te de la meva química i mostrar sempre interès en el que faig i per ser-hi sempre que ho he necessitat per anar al cine, a passejar a la Duna o per anar a fer un gelat. Padrí i padrina aquest és el llibre que em farà doctor, però no dels que curen persones, us vull donar les gràcies per tots els sopars, dinars , berenars, partides de cartes i de parxís que hem gaudit plegats. Tieta Montse, tiet Xavi, tieta Nati moltes gràcies. A la meva cosina Nekane per les xarrades que hem tingut sobre el doctorat entre nosaltres i amb la família, et desitjo lo millor en la teva recta final que com pots veure sempre arriba.

A tots vosaltres moltes gràcies per ser-hi ja que tot aquesta etapa tant important de la meva vida sense vosaltres de ben segur que no hagués esta el mateix.

Sempre a punt i tant com puc.

AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL

Marc Garcia Civit

"Try not to become a man of success,

but rather try to become a man of value."

Albert Einstein

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

Table of contents

Chapter 4: 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

Chapter 5: Conclusions

Chapter 6: Experimental Part

Chapter 7: Summary

Appendix

Lists of abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
Å	Ångström
AIBN	Azobisisobutyronitrile
APCI	Atmospheric-pressure chemical ionization
Ar	Aromatic group
atm	Atmosphere
B3LYP	Becke, three-parameter, Lee-Yang-Parr/
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BBD	borabicyclo(3.3.2)decane
Bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl group
Bu	Butil group
Bz	Benzoate
^{c}Hex or Cy	Cyclohexyl group
Conv.	Conversion
dan	1,8-diaminonaphthalene
DCM	Dichloromethane
DFT	Density functional theory
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
E	Electrophilic reagent
e.e.	Enantiomeric excess
EI	Electron ionization
equiv.	Equivalent
ESI	Electrospray ionization
esp	$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionic acid

Abbreviations

Abbreviations

Et	Ethyl group
eV	Electronvolt
g	gram
HMPA	Hexamethylphosphoramide
HSQC	Heteronuclear single quantum coherence spectroscopy
Hz	Hertz
I.Y.	Isolated Yield
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium
IPr	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium
^{i}Pr	*Iso*-propyl group
Kcal	kilocalorie
LSB	LaNa$_3$-tris(binaphthoxide)
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
M	Molar
Me	Methyl group
mG	Milligram
Min	Minute
mL	Milliliter
mmol	Millimol
MPa	Megapascal
MS	Molecular sieves
MW	Microwave
NHC	N-Heterocyclic carbene
^{n}Pent	Linear pentyl group
Nu	Nucleophile
OAc or AcO	Acetyl group
ºC	Celsius Degrees
Ph	Phenyl group

2

phen	1,10-phenanthroline
pin	Pinacol
ppm	Parts per million
Pr	Propyl group
PS-BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine supported on polystyrene
S-PTTL	N-phthaloyl-(*S*)-*tert*-leucinato
r.t.	Room temperature
S_N	Nucleophilic substitution
TBAF	Tetrabutylammonium fluoride
^{t}Bu	*tert*-Butyl
THF	Tetrahydrofurane
TMAF	Tetramethylammonium fluoride
TMS	Trimethylsilyl group
TOF	Time-of-flight
Tol	Tolyl group
UV	Ultraviolet light
ZPC	Zero-point correction

4

"Look wide, and even when you think

you are looking wide - look wider still."

Sir. Robert Baden-Powell

Chapter 1

Introduction and Objectives

1.1. Context of the thesis

Straightforward synthetic methods for carbon-heteroatom bond formation are of great demand in organic synthesis and have attracted the interest of many chemist, leading them to develop new methodologies for these transformations. Metal-catalyzed transformations have become a powerful tool in modern organic synthesis to construct new bonds with high selectivity under mild reaction conditions.[1] The selective formation of C-B, C-N, C-O, C-Si, C-P and C-Sn are known from 1970[2] while the formation of C-S and C-Se was not so well explored because sulfur and selenium compounds were considered catalyst poisons.[3,4] This problem has been successfully solved, and in recent decades, several excellent catalytic systems have been found to develop the synthesis of organosulfides and organoselenides, leading to the development of practical procedures for organic synthesis.[5]

In this context, this thesis focuses on the selective synthesis of C-S and C-Se bonds by using chalcogenoboranes pinB-YAr (Y = S and Se) as reagents. Taking advantage of the Lewis acidic properties of the boron atom, the addition of pinB-YAr to unsaturated substrates has been carried out in the absence of transition metal complexes. In the following sections, we describe the importance of molecules containing C-S and C-Se, the methodological background of the synthesis of C-S and C-Se bonds, as well as the preparation and reactivity of B-S and B-Se reagents.

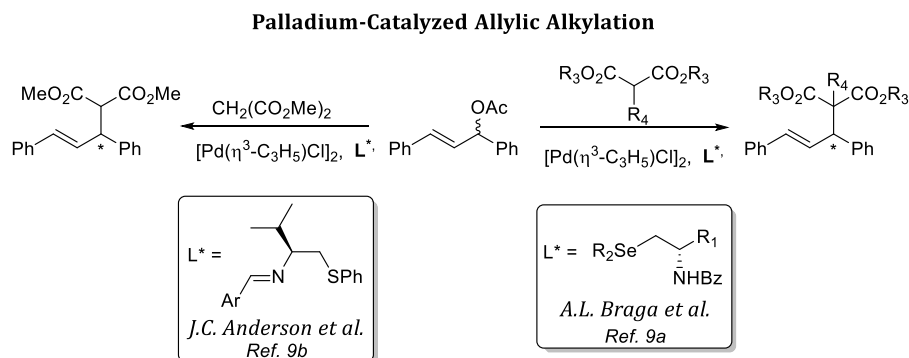## 1.2. Interest of organoselenides and organosulfides

Organic sulfides and selenides represent an important class of compounds due to their direct application in chemistry, biology, medicine, and material science.[6]

1. Introduction and Objectives

The richness of organoselenides and organosulfides compounds and their structural and electronic diversity, as well as they specific chemical behavior, make them versatile reagents in chemistry. For example, they can be used in nucleophilic, electrophilic and radical reactions.[7] In the next section, their applications as ligands or as bioactive compounds is highlighted.

1.2.1 Organoselenides and organosulfides as ligands

In transition-metal catalysis, ligands based on organoselenides and organosulfides, have undergone considerable development due to their coordination abilities to a variety of transition metals and their better stability in air and moisture in comparison to those which have phosphorous donors.[8] As an example, in the palladium-catalyzed allylic alkylation it has been reported that ligands based on organoselenides and organosulfides have soft-soft interactions between the chalcogens and the palladium metal (Scheme 1.1).[9]

Scheme 1.1 Example of ligands based on organoselenides and organosulfides in allylic alkylation catalyzed by palladium complexes.

8

1.2.2 Organoselenides and organosulfides as bioactive compounds

Many organochalcogenides have shown bioactive properties in biology and medicine. For mostly of living organisms, the organosulfides such as amino acids (cysteine (**I**) and methionine (**II**)), peptides (glutathione (**III**)), as well as protein cross-linking agents (biotin (**IV**)), play and important role.[10] In addition to this, organosulfur moieties are also present in synthetic drugs such as the antibiotics penicillin G (**V**) and amoxicillin (**VI**).[11] Also some 1,3-biarylsulfanyl derivatives have been reported as new anti-breast cancer agents (Figure 1.1).[12]
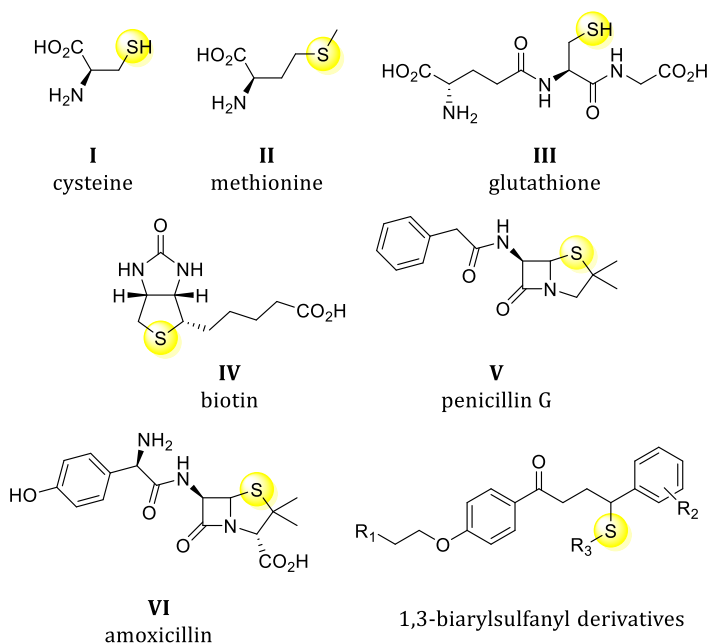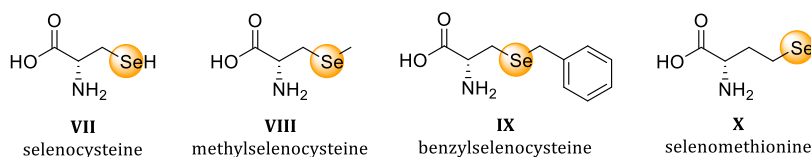

Figure 1.1 Bioactive organosulfur compounds present in nature and drugs.

Because of their antioxidant character, organoselenides have been widely studied and tested in biological processes such as inhibitors[13], enzymes[14] and even as therapeutic agents.[15]

1. Introduction and Objectives

Amino acids derivatives from selenocysteine **VII,** such as methylselenocysteine **VIII** and benzylselenocysteine **IX,** possess chemopreventive activity in animal tumor models.[16] Also selenomethionine **X** has been under study for its neuroprotective action suggesting its potential use as therapeutic agent in neurodegenerative disease (Figure 1.2).[17]

VII
selenocysteine

VIII
methylselenocysteine

IX
benzylselenocysteine

X
selenomethionine

Figure 1.2 Bioactive organoselenides

The relevant role of organoselenides and organosulfides as synthons and bioactive compounds, has lunched the interest in new synthetic methods to prepare them.

## 1.3. Synthetic methods for C-S and C-Se bond formation

To fulfill the increasing demand on organosulfides and organoselenides, several approaches have focused on new general methods to introduce sulfur and selenium moieties to organic molecules. The developed catalytic methods can be classified in two main groups: transition metal-catalyzed methods and organo-catalyzed methods. Concerning the transition metal-catalyzed methods, the most used are the ones involving cross-coupling chemistry and addition reactions. Metal-catalyzed reactions are the most efficient for the formation of $C(sp^2)$-Y and $C(sp)$-Y bonds (Y=S and Se), because nucleophilic substitutions on the $C(sp^3)$ atoms does not require a metal catalyst. Alternatively, organocatalysis has become a plausible tool organoselenides and organosulfides synhtesis.

10

1.3.1. Transition metal-catalyzed approaches

1.3.1.1. Cross-coupling reactions

Cross-coupling chemistry is a widely-recognized approach to synthesize new C-Y bonds (Y = S and Se). To form this kind of bonds, an organic halide reacts with RYH, R_2Y_2 or RYM' catalyzed in the presence of a low valence metal complex.

The general mechanism, shown in Scheme 1.2, is well-known and the catalytic cycle includes the following stages: first the oxidative addition of an organic halide R-X to the metal center, followed by a transmetalation with RY-Z (Y = S, Se) and (Z = H, YR or M'), and finally a C-heteroatom reductive elimination to generate the desired product and regenerate the metal complex. In this transformation, a salt is generated as byproduct.
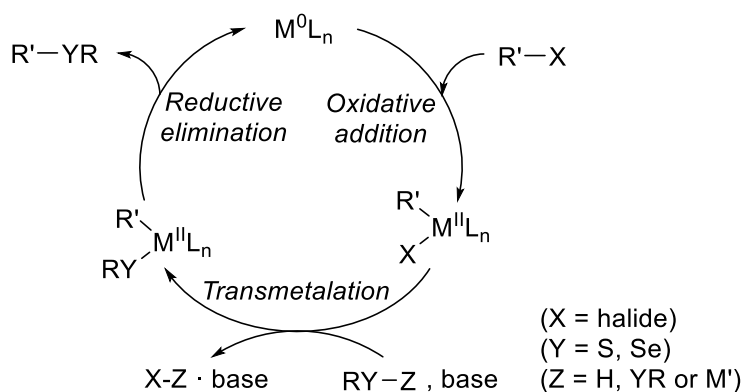

Scheme 1.2 General catalytic cycle for cross-coupling reactions to form C-S and C-Se bonds.

One of the most used metals for cross-coupling reactions is palladium.[18-19] The first successful reaction for synthesizing diaryl sulfides and arylalkyl sulfides in moderate to good yields was demonstrated in 1978 using $Pd(PPh_3)_4$ by Kosugi, Shimizu and Migita.[20] This methodology was further extended to vinyl halides and was found to be a stereospecific reaction with retention of the double bond configuration (Scheme 1.3, *a*).[21]

11

1. Introduction and Objectives

A reported way to synthesize unsymmetrical RSR' sulfides consists in a palladium-tetrakis(triphenylphosphine) catalyzed cross-coupling of the silyl derivative of the thiols R_3SiSH with vinyl halides. The formation of the vinyl silylsubstituted sulfides intermediates allows the further functionalization by alkylation or Pd-catalyzed alkenylation to end up with unsymmetrical sulfides (Scheme 1.3, *b*).[22]
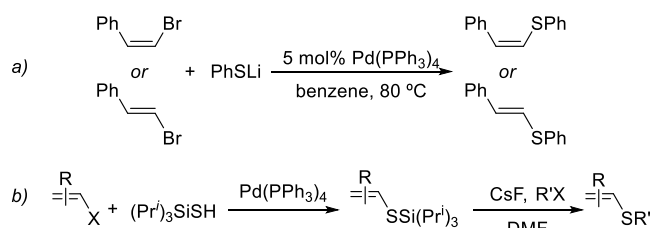

Scheme 1.3 Synthesis of vinyl sulfides through palladium cross-coupling.

Later, in 2002, Li and co-workers proposed an air stable phosphine oxide $^tBu_2POH$ as an efficient ligand for palladium catalyzed C-S cross-coupling reactions. By using this catalytic system, they have been able to react RSH with 1-chloro-1-cyclopentene (Scheme 1.4).[23]
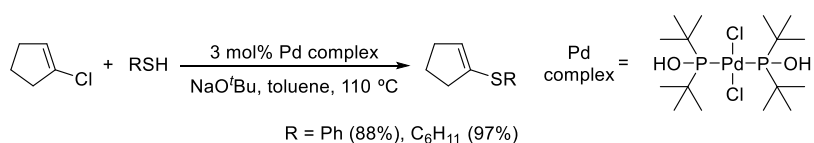
Scheme 1.4 Air-stable palladium-catalyzed C-S bond formation of vinyl chlorides.

The palladium cross-coupling methodology has also been used to synthesize benzothiophenes, which form the core of medicinally important molecules, such as raloxifene[24] and zileuton.[25] A cascade reaction, *via* intramolecular S-thiophenylation and cross-coupling, allows *gem*-dihalovinyl thiophenol to form vicinal C-S and C-C bonds (Scheme 1.5).[26]
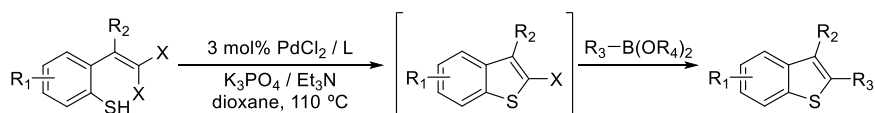
**Scheme 1.5** Synthesis of benzothiophenes by Pd-catalyzed vinylic C-S Coupling.

In(I) has been reported as a good reducing agent for compounds with formula (PhY$_2$) (Y = S and Se). After oxidative addition, the complex [In(III)(YPh)$_2$I] acts as the transmetalation reagent for a Pd-catalyzed cross-coupling.[27] This reaction shows to be stereospecific for *E*-isomers but not for the *Z*-isomers due to a possible β-elimination pathway (Scheme 1.6).
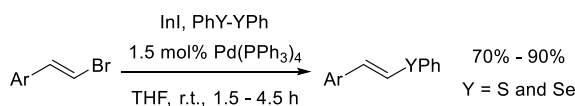
Scheme 1.6 In(I) iodide promoted cleavage of (PhY)$_2$ and subsequent Pd-catalyzed cross-coupling.

The observations reported by Ullmann *et. al.*[28] about the coupling properties of metallic Cu, opened the implementation of novel cross-coupling approaches in synthesis.[29] These have allowed to develop also Cu-catalyzed cross-couplings to synthesize C-S and C-Se bonds.

The first reaction between unactivated aryl iodides and aryl thiols catalyzed by copper iodide in hexamethylphosphoramide (HMPA) were reported by H. Suzuki and co-workers.[30] The same copper(I) iodide was used for the arylselenylation of aryl bromides and iodides by Beletskaya and co-workers using tin derivatives of the type Ar'SeSnBu$_3$ (Scheme 1.7).[31] This system proved to be better than the Pd-catalyzed ones in terms of higher product yields and the absence of the disproportionation product Ar$_2$Se.
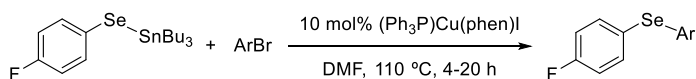

**Scheme 1.7** Synthesis of unsymmetrical arylselenides by copper(I) cross-coupling.

1. Introduction and Objectives

James M. Cook and co-workers developed a methodology for copper(I)-catalyzed formation of vinylic carbon-sulfur bonds at mild reaction conditions with low cost catalyst system. The desired vinyl sulfides were obtained with full retention of stereochemistry (Scheme 1.8, a).[32] In 2010 they extended the scope of the catalytic system. Under the same mild reaction conditions, they could perform the Cu-catalyzed cross-coupling of (Z)-Ethyl-3-iodoacrylate with aromatic, aliphatic, and heterocyclic thiols (Scheme 1.8, b).[33]
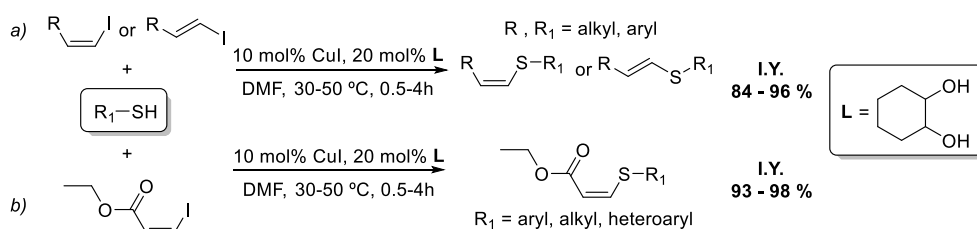
**Scheme 1.8** Mild reaction conditions for Cu(I) cross-coupling towards C-S bonds.

The *L*-proline amino acid has been used as ligand in cross-coupling reactions.[34] For that reason it has been used in copper-catalyzed cross-coupling to synthesize vinyl sulfides and vinyl selenides. It was reported by Yuan and co-workers that the CuI/L-proline system was able to catalyze the coupling of 3-iodo-cyclohexenone with a variety of aryl thiols in ethanol at reflux (Scheme 1.9).[35]
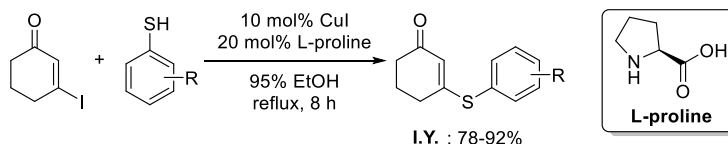
Scheme 1.9 Cross-coupling of 3-iodo-cyclohexanone with aryl thiols catalyzed by CuI/L-proline system.

By using the same system, Bao and co-workers reported the synthesis of *E*-vinyl selenides by coupling vinyl bromides with dialkyl selenides or diaryl selenides. This methodology was performed in ionic liquids and requires the

14

use of Zn as the reducing agent for generating the transmetalation agent (Scheme 1.10).[36] The route for the *Z*-vinyl chalcogenides was also reported by the same group with a similar system.[37]
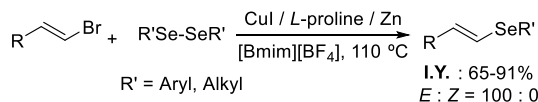
Scheme 1.10 Cross-coupling of vinyl bromides with (R'Se)$_2$ catalyzed by CuI/*L*-proline system.

1.3.1.2. Addition reactions

Alternative metal-catalyzed methods to introduce the sulfur and the selenium atom into organic molecules involves addition reactions. By the addition reaction of R$_2$Y$_2$ or RYH (Y = S and Se) to alkynes or allenes, new C-Y bonds are formed. The general catalytic cycle for the addition methods is shown in the Scheme 1.11 and it is form by the following steps: first the oxidative addition of R$_2$Y$_2$ or RYH to metal center with low oxidative state, followed by the alkyne coordination and insertion into M-Y bond or M-H. Eventually, the reductive elimination provides the C-S or C-Se bond. The main difference with the cross-coupling mechanism is that in the addition reaction no transmetalation occurs. For that reason, a 100% of atom economy is achieved and leads to an advantage in terms of Green Chemistry.
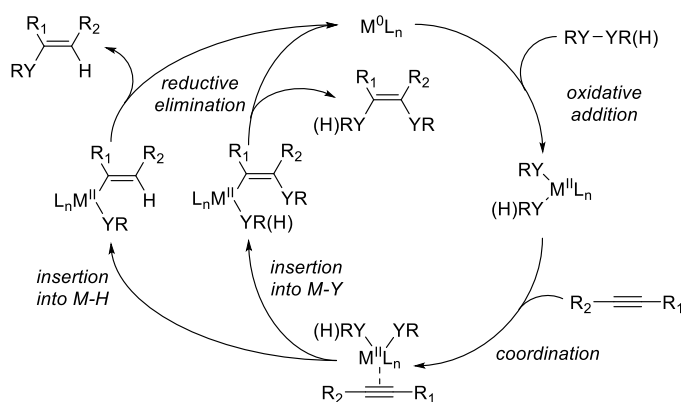
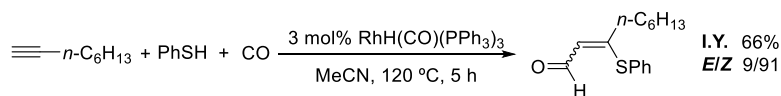**Scheme 1.11** General catalytic cycle for addition reactions.

1. Introduction and Objectives

The metal-catalyzed additions to triple bonds and allenes proceed in a stereoselective way and forms exclusively the *syn*-addition products. In the case of the thiols and selenols a regioselectivity issue must be solved. The insertion can take place into the M-Y or the M-H bond and subsequently lead to different regioisomers as is shown in the Scheme 1.11.

The regioselectivity depends on the metal complex, the type of the alkyne/allene (internal or terminal), and the nature of the substituents R_1 and R_2.[38]

The most used metals in the addition of thiols and selenols to terminal and internal triple bonds to form vinyl-chalcogenides products are Pd,[39] Ni,[40] Rh,[41-42], and Ir[42] among others.

In 2003, Ogawa and co-workers reported the synthesis of β-thio-α,β-unsaturated aldehydes through a rhodium(I) thioformylation of terminal alkynes. In the presence of a catalytic amount of $RhH(CO)(PPh_3)_3$, $RhCl(PPh_3)_3$, and $RhCl(CO)(PPh_3)_2$, under the pressure of CO (3 MPa) at 120 °C in CH_3CN terminal alkynes reacted with PhSH, to provide the desired products in good yields (Scheme 1.12).[43] Their mechanistic proposal includes the formation of the rhodium sulfide complex $[Rh(SPh)(CO)(PPh_3)_2]$ as the key species in the addition reaction mechanism.

$$\equiv\!\!-n\text{-}C_6H_{13} + PhSH + CO \xrightarrow[\text{MeCN, 120 °C, 5 h}]{\text{3 mol\% RhH(CO)(PPh}_3)_3}$$

n-C$_6$H$_{13}$

O=
H   SPh

I.Y. 66%
E/Z 9/91

**Scheme 1.12** Rhodium catalyzed synthesis of β-thio-α,β-unsaturated aldehydes.

The addition of thiols and selenols to allenes has also been reported. With $Pd(OAc)_2$ catalyst, Ogawa and co-workers were able to synthesize the vinyl sulfides and vinyl selenides in good to high yields (Scheme 1.13).

16

The addition of the sulfur and selenium took place in the internal double bond of the allene.[44]
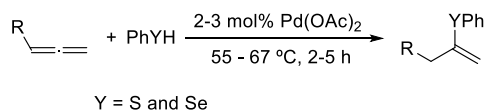
Y = S and Se

Scheme 1.13 Palladium catalyzed addition of thiols and selenols to allenes.

The same group also reported the addition of benzenethiol to cyclohexylallene catalyzed by Pd(PPh₃)₄. The reaction was carried out in acetonitrile and affords regioselectively the corresponding terminal vinylic sulfide in good yield, whereas Pt(PPh₃)₄-catalyzed hydrothiolation of cyclohexylallene gives the regioisomeric vinyl sulfide successfully (Scheme 1.14).[45]
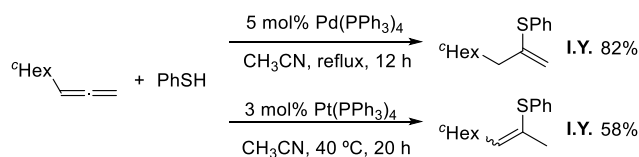

Scheme 1.14 Addition of benzenethiol to cyclohexylallene catalyzed by palladium and platinum complexes.

Dichalcogenides can be added to alkynes mainly under Pd metal-catalyzed reactions and in less extension Ni or Rh complexes have been used.

In 1991, Ogawa and co-workers reported the Pd(PPh₃)₄ catalyzed addition of Ph₂S₂ and Ar₂Se₂ to terminal alkynes giving good yields (up to 98%). The reaction showed high selectivity towards the *Z*-isomers. However, for R₂Y₂ (R = alkyl) this methodology showed low yields. In the same work, they also reported that under CO pressure the reaction generates *β*-thio-*α*,*β*-unsaturated thioesters and *β*-seleno-*α*,*β*-unsaturated selenoesters (Scheme 1.15).[46]
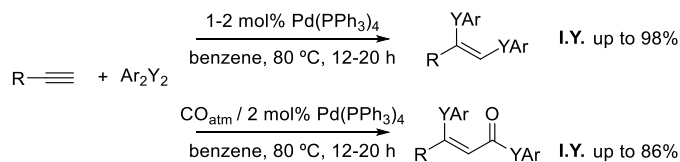
Scheme 1.15 Addition of diaryldichalcogenides to terminal alkynes catalyzed by tetrakis(triphenylphosphino) palladium (0).

The same group reported the use of the CO/Pd(PPH$_3$)$_4$ with diaryldichalcogenides and terminal propargyl alcohols. At the end of the reaction they obtained β-substituted-α,β-lactones in good yield (Scheme 1.16,a).[47] Moving to internal homopropargyl alcohols, The Ar$_2$S$_2$ addition provides different lactones (Scheme 1.16,b).[48] In the case of propargyl alcohols first the addition took place and later the carboxylation but in the homopropargyl alcohols the order comes in the other way round.
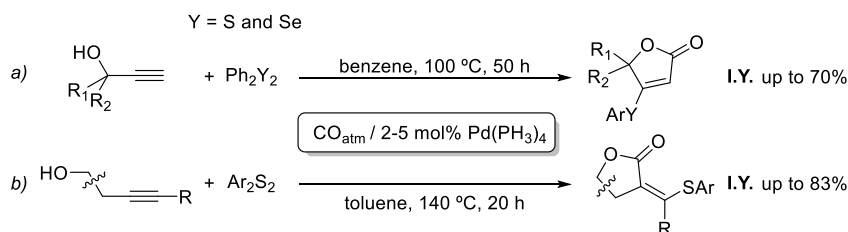
Scheme 1.16 Palladium catalyzed synthesis of β-substituted-α,β-lactones.

1.3.2. Organocatalytic approaches

Organocatalysis is a relatively new field which uses small organic molecules to catalyze organic transformation. Its main use is in asymmetric synthesis.[49] The main advantages of organocatalysis are the use of insensitive to air and moisture catalysts, and in the asymmetric synthesis they can provide both enantiomers with high enantioselectivity.[50]

Concerning the organocatalytic C-S bond formation several strategies have been developed such as: Sulfa-Michael reactions (1,2-, 1,6-, and γ-additions of sulfur nucleophiles), desymetrization reactions, sulfenylation

methodologies, ring-opening procedures and thioesterification reactions, among others.[51]

In 1951, Caston and Wanser demonstrated that the sole addition of a catalytic amount of piperidine, was enough to catalyze the 1,4-addition of aryl and benzyl thiols to nitroalkenes in 51% to 100% yields.[52] After that many other have used organocatalysis to promote the C-S bond formation in Michael acceptors. Remarkably, the works by Ménand and co-worker[53] and Toma and co-workers,[54] described two different protocols to perform sulfa Michael addition to a wide variety of α,β-unsaturated ketones, esters, aldehydes, nitriles and nitroolefins, in moderate to quantitative yields.

Ménand and co-workers reported the addition of alkyl and aryl thiols to unsaturated acceptors in moderate to high isolated yields with 2-4 mol% of TMAF (tetramethylammonium fluoride)at room temperature in acetonitrile (Scheme 1.17,a).[53] In the case of Toma and co-workers the reaction was catalyzed by 5 mol% of L-proline at room temperature in a maximum of 2 hours with alkyl, aryl and heteroaryl thiols. They used the ionic liquid [Bmim]PF_6 because by a simple extraction with an organic solvent the products were separated from catalyst (Scheme 1.17,b). [54]
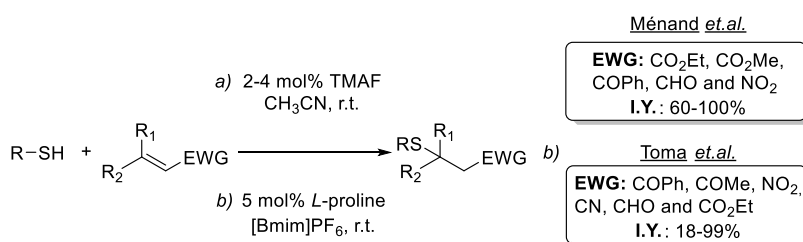

Scheme 1.17 Organocatalytic sulfa Michael addition

In order to increase the recovery and recyclability of the organocatalyst, the development of new polymer-supported material has been launched.[55]

1. Introduction and Objectives

In that context, Vaccaro and co-workers developed a new methodology catalyzed by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP), under solvent free conditions. They used alkyl and aryl thiols in the addition to α,β-unsaturated ketones and esters at 60 ºC obtaining the desired product in quantitative yields (Scheme 1.18). They were able to use this supported organocatalyst under batch conditions and be able to reuse the catalyst up to 5 runs without decrease of its efficiency. With extension of the application to continuous-flow system.[56]
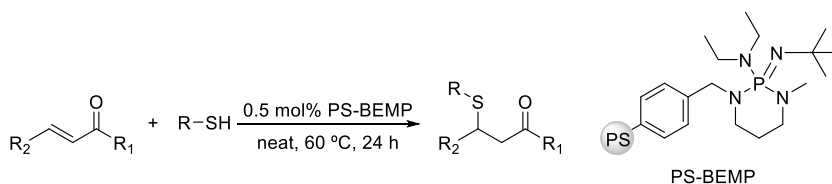
**Scheme 1.18** Supported catalyst for thiol addition to conjugated ketones and ester.

Concerning the α-functionalization, in 2016 the group of Chen reported a IMes catalyzed methodology to generate a new C-S bond in α,β-unsaturated aldehydes. In this case, an electrophilic sulfur precursor as *N*-(phenylthio) phthalimide was used in DMF at room temperature (Scheme 1.19).[57]
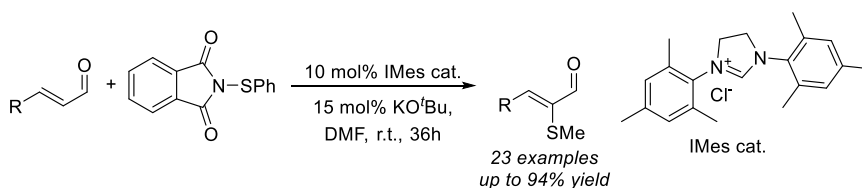
**Scheme 1.19** *N*-heterocyclic carbene catalyzed α-sulfenylation of α,β-unsaturated aldehydes.

The suggested mechanism for this transformation follows the next steps: first the nucleophile NHC attacks the β-position leaving a negative charge in the α-position, that interacts with the electrophilic sulfur in the reagent.

20

The base assistance to the 3,4-disubstituted intermediate, favors the proton abstraction and recovery of the NHC catalyst (Scheme 1.20).
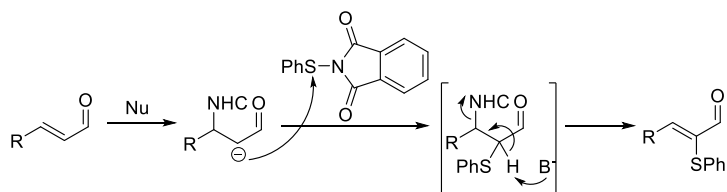
Scheme 1.20 Mechanistic proposal for NHC catalyzed α-sulfonylation.

By using the analogue electrophilic selenium reagent, *N*-(phenylseleno) phthalimide, Guo, Wang and co-workers were able to perform the α-selenation of aldehydes and ketones. They used 2 mol% of L-prolinamide to synthesize the α-seleniated products in high to quantitative yields (Scheme 1.21).[58]
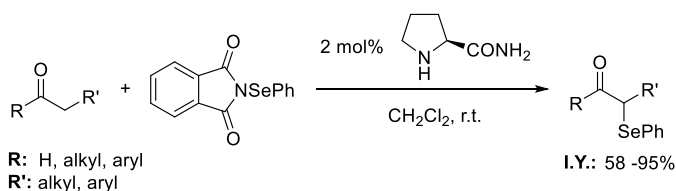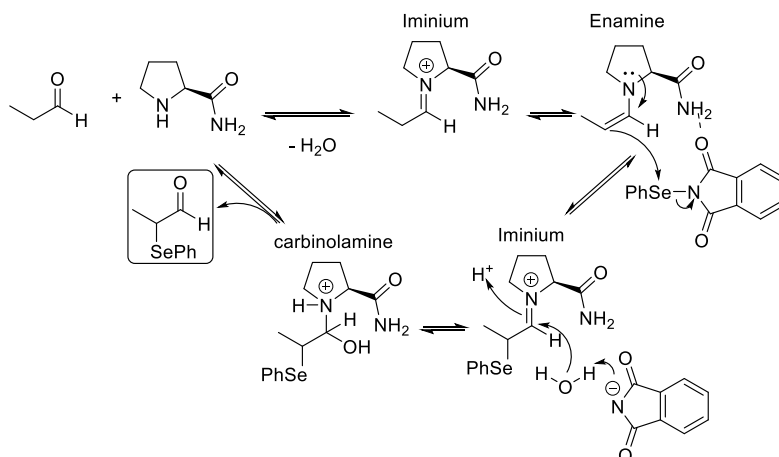

Scheme 1.21 Aldehyde and ketone α-selenenylation reactions promoted by *L*-prolinamide organocatalysts.

They also performed some theoretical analysis of *L*-prolinamide catalyzed α-selenenylation reactions of aldehydes by DFT calculations. The initial step is the formation of the enamine intermediate which then undergoes an attack at the electrophilic selenium atom. Formation of the Se-C bond takes place in concert with departure of phthalimide anion to produce the α-selenoiminium ion intermediate. Eventually, protonation of the phthalimide nitrogen with water, favors the hydroxy attack to the iminium carbon to produce a carbinolamine, which deliver the α-selenoaldehyde product (Scheme 1.22).[58]

1. Introduction and Objectives

Scheme 1.22 Proposed mechanism for aldehyde and ketones α-selenenylation reactions, catalyzed by *L*-prolinamide.

1.4. Synthesis and reactivity of pinB-SAr and pinB-SPh

Molecules containing B-S or B-Se bonds are of great value in synthetic chemistry due to the presence of a strong Lewis acid component next to a soft Lewis base. A novel family of B-Y species (Y = S, Se) was developed and patented in 2006 by Wescott's group but it's reactivity was not further explored.[59] In 2013, more examples of B-S and B-Se compounds were added to this family of bifunctional systems by the Nolan's group.[60]

These species were prepared under inert atmosphere by metal catalyzed dehydrogenative borylation of the corresponding thiol or selenol and one equivalent of pinacolborane (HBpin).[59-60] By using 2.5 mol% of the Wilkinson's catalyst [RhCl(PPh$_3$)$_3$][59] or [RhCl(PPh$_3$)$_3$(3-phenylindenyl)][60], complete conversion of the starting materials was achieved selectively at room temperature, in 16 hours (Scheme 1.23).
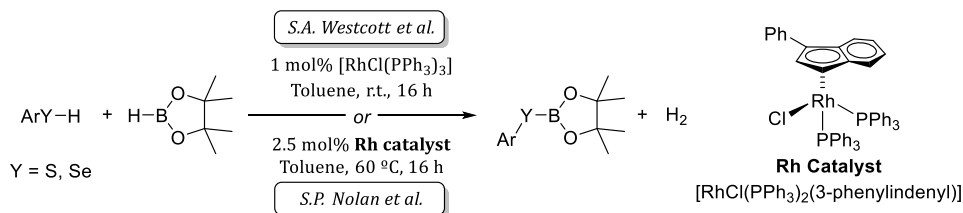
Scheme 1.23 Synthesis of the pinB-SAr and pinB-SeAr reagents by rhodium-catalyzed dehydrogenative borylation.

The pinB-SPh (**1**), pinB-STol (**2**), pinB-SBn (**3**) and pinB-SePh (**4**) species were successfully prepared and characterized using several 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 three-coordinated Bpin.[59-60]

The species **2** and **4** were also characterized by a single crystal X-ray diffraction study.[59] The S-B distance of 1.823 Å and the Se-B of 1.950 Å are somewhat longer compared to the B-B distance in the B_2pin_2 (1.678 Å).[61] In addition, these compounds appeared to be very sensitive to the air and moisture. They decompose rapidly to disulfides and diselenides plus multiple boron containing by-products if exposed to open air. This fact reflects that the reagents are very reactive. Despite their high reactivity, it is surprising that the reported examples based on their reactivity are scarce.

In 1985 a study by Leonard and Livinghouse showed that novel monomeric selenium boron compounds, derived from dialkylboranes, could be used for the synthesis of organoselenides.[62] By mixing 9-borabicyclo[3.3.1]nonane (9-BBN) or diisopinocampheylborane with 1 equiv. of the benzeneselenol in toluene and stirring it for 5 h at 50 ºC they manage to synthesize the desired selenoborinate (Scheme 1.24). They reported the sensitivity of this compound to both oxygen and moisture and for that reason they never isolate it, they just store it as a stock solution in dark.

23

1. Introduction and Objectives
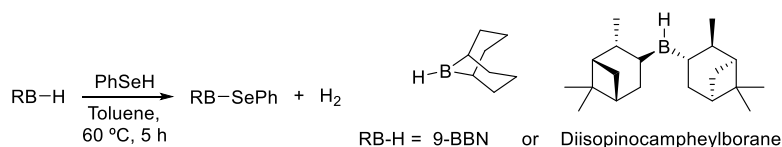
Scheme 1.24 Synthesis of the first selenoborinate compounds

9-(Phenylseleno)-9-borabicyclononane was found to react with a variety of α,β-unsaturated ketones to form the 1,4-boron enolate at room temperature (Scheme 1.25, *a*).[62] They observed that by adding a radical inhibitor as galvinoxyl the reaction was not depressed and by adding a radical initiator as AIBN under irradiation the reaction was not enhanced proving that the additions might not follow a radical mechanism. In the case of 4,4-dimethyl-2-cyclopenten-1-one at -78 °C only the 1,2-adduct was observed and by increasing the temperature to room temperature was smoothly converted to the corresponding 1,4-boron enolate (Scheme 1.25, *b*).
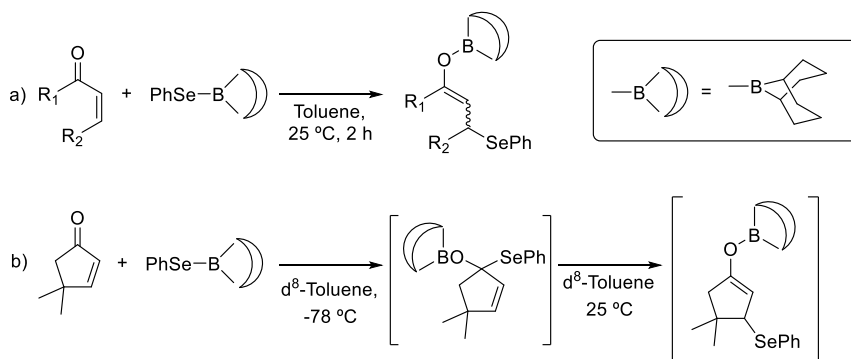
**Scheme 1.25** Reactivity of selenoborinate with α,β-unsaturated ketones

In 1993 Miyaura and Suzuki reported the first palladium(0)-catalyzed addition reaction of the 9-(alkylthio)-9-BBN derivatives to terminal alkynes to produce (β-alkylthio)vinylboranes. It has been reported that the reaction takes place in high yields with control on the regio- and stereoselectivity (Scheme 1.26).[63]

24
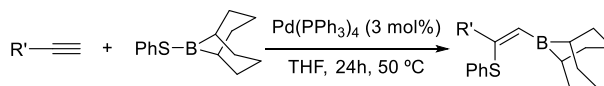
Scheme 1.26 Miyaura and Suzuki's palladium-catalyzed thioboration of alkynes

Miyaura and Suzuki postulated a thioboration mechanism concerning an oxidative addition of the S-B bond to the Pd(0) as the first step even though they have no direct evidence that S-Pd^{II}-B species exists. The mechanism postulated follows with the insertion of the alkyne into the sulfur-palladium bond and ends up with the reductive elimination of the alkenylboron compound through a regio- and stereoselective manner (Scheme 1.27).
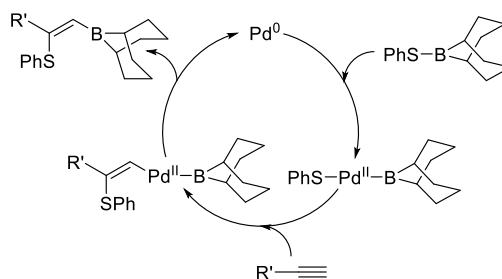

Scheme 1.27 Miyaura and Suzuki's mechanism proposal for the palladium-catalyzed alkyne thioboration

Some years later, in 1998, Musaev and Morokuma proposed another mechanism for the Pd(0) catalyzed thioboration of terminal alkynes supported by DFT calculations. According to their calculations, the oxidative addition of B-S bond to Pd(0) cannot take place, for that reason they proposed analternative mechanism concerning a metathesis pathway.[64]

The initial step is the coordination of the alkyne to the Pd forming a π-complex followed by a dissociation of one phosphine. Intermolecularly, the B-S reagent attacks Pd π-complex. The sulfur atom is bonded to the metal and the B is bonded to the carbon, an extra stabilization is achieved by the interaction of one of the oxygens in the pinacol moiety with the vacant in the metal center.

25

1. Introduction and Objectives

After the metathesis, the sulfur moiety and the olefin are in a *trans*-conformation so a sulfur migration takes place to achieve the *cis* conformation. Then a phosphine coordinates, to cover the vacancy and the metal complex achieve a typical square-planar geometry. Finally, the reductive elimination takes place where the Pd-S and the Pd-C are cleavage to form the new C-S bond (Figure 1.3).
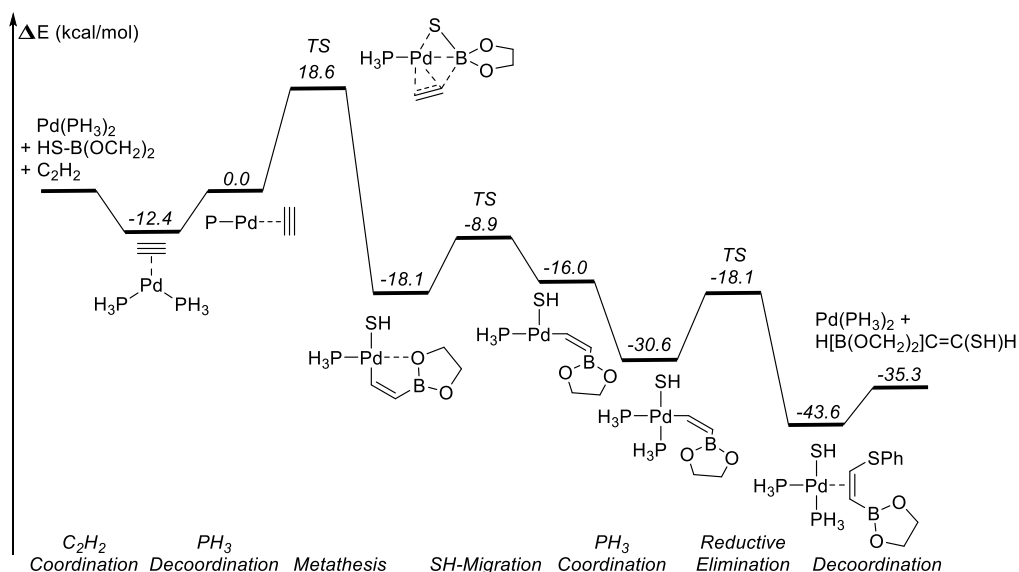
Figure 1.3 Potential-energy profile (without ZPC) of Musaey and Morokuma's mechanism proposal for palladium-catalyzed alkyne thioboration calculated at the B3LYP/BSII level.

1.6. Objectives

<u>Main Objective:</u>

The thesis is aimed to take advantage of the "*pull-push*" effect of the B in the B-Y reagents (Y = S and Se), to selective add the sulfur or selenium moieties to unsaturated substrates to generate a new methodology towards the synthesis of organosulfides and organoselenides.

<u>Specific Objectives:</u>

*Objective 1:* To synthesize β-sulfido carbonyl compounds through the thioboration of α,β-unsaturated ketones and aldehydes with B-S reagents (pinB-SPh, pinB-STol and pinB-SBn) in a transition metal-free context (Scheme 1.28, *a*).

Objective 2: To study the reactivity of ynones with pinB-SePh, pinB-SPh and pinB-SBn, to promote the synthesis of stereoselective vinyl selenides and vinyl sulfides in a transition metal-free context (Scheme 1.28, *b*).

Objective 3: To experimentally explore the pinB-SePh addition to α,β-acetylenic esters towards the β-selenation (Scheme 1.28, *c*) as well as the use of PR_3 as an additive to promote the plausible 3,4-selenoboration to synthesize α-substituted organoselenides (Scheme 1.28, *c'*).

Objective 4: To develop a method for the insertion of the diazo compound Me_3SiCHN_2 into B−S bonds to promote a direct synthesis of main group, multisubstituted sp^3 carbons (Si, B, S) and further functionalization through base-mediated alkylation (Scheme 1.28, *d*).

Chapter 1

1. Introduction and Objectives
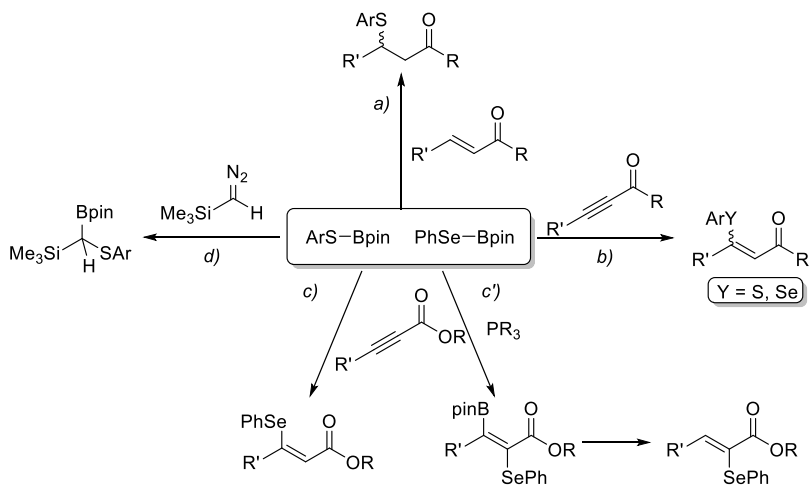
Scheme 1.28 Transition metal-free reaction of the pinB-YAr reagents with different substrates.

1.7. References

1   a) K. C. Nicolaou, C. R. H. Hale, C. Nilewskia, H. A. Ioannidou, *Chem. Soc. Rev.* **2012**, *41*, 5185–5238; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; c) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250; d) J. -H. Xie, S. -F. Zhu, Q. -L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; e) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943; f) S. Ikeda, *Acc. Chem. Res.* **2000**, *33*, 511–519; g) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864–6900; h) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; i) A. Padwa, *Chem. Soc. Rev.* **2009**, *38*, 3072–3081; j)H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; k) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; l) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; m) M. M. Heravi, E. Hashemi, *Tetrahedron* **2012**, *68*, 9145–9178.

2   a) I. Beletskaya, C. Moberg, *Chem. Rev.* **2006**, *106*, 2320–2354; b) T. E. Mìller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; d) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159; e) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783–1826; f) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; g) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; h) M. Suginome, Y. Ito, *Chem. Rev.* **2000**, *100*, 3221–3256; i) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746–1787.

3   L. L. Hegedus, R. W. McCabe, *Catalyst Poisoning,* Marcel Dekker: New York, **1984**.

4   J. Dunleavy, *Platinum Met. Rev.* **2006**, *50*, 154-155

5   a) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596-1636; b) N. V. Orlov, *ChemstryOpen* **2015**, *4*, 682-697; c) T. Kondo, T. -A. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205-3220; d) D. M. Freudendahl, S. A. Shahzad, T. Wirth, *Eur. J. Org. Chem.* **2009**, *11*, 1649-1664.

6   a) S. A. Vizer, E. S. Sycheva, A. A. A. Al Quntar, N. B. Kurmankulov, K. B. Yerzhanov, V. M. Dembitsky, *Chem. Rev.* **2015**, 115, 1475–1502; b) P. Chauhan,

1. Introduction and Objectives

S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807–8864; c) M. Godoi, M. W. Paixão, A. L. Braga, *Dalton Trans.* **2011**, *40*, 11347-11355; d) A. J. Mukherjee, S. S. Zade, H. B. Singh, R. B. Sunoj, *Chem. Rev.* **2010**, *110*, 4357–4416; e) A. Kumar, G. K. Rao, F. Saleem, A. K. Singh, *Dalton Trans. 2012*, *41*, 11949-11977; f) F. Marini, S. Sternativo, *Synlett* **2013**, *24*, 11-19.

7   a) M. Godoi, M. W. Paixão, A. L. Braga, *Dalton Trans.* **2011**, *40*, 11347-11355; b) F. Aida, K. Oyaizu, *Chem. Lett.*, **2016**, *45*, 102-109.

8   *For ligands based on organoselenides:* A. Kumar, G. K. Rao, F. Saleem, A. K. Singh, *Dalton Trans.* **2012**, *41*, 11949-11977. *For ligands based on organosulfides:* a) H. Pellissier, *Tetrahedron* **2007**, *63*, 1297-1330; b) M. Mellah, A. Voituriez, E. Schulz, *Chem. Rev.* **2007**, *107*, 5133–5209.

9   a) A. L. Braga, F. Vargas, J. A. Sehnem, R. C. Braga, *J. Org. Chem.* **2005**, *70*, 9021-9024; b) J.C. Anderson, D. S. James, J. P. Mathias, *Tetrahedron: Asymmetry* **1998**, *9*, 753–756.

10 J. R. Fraústo da Silva, R. J. P. Williams, *The Biological Chemistry of the Elements;* Oxford University: New York, **2001**.

11 a) A. Nudelman, *The Chemistry of Optically Active Sulfur Compounds*; Gordon and Breach: New York, **1984**. b) L. A. Damani, *Sulfur-Containing Drugs and Related Organic Compounds*; Wiley: New York, **1989**.

12 A. Kumar, V. D. Tripathi, P. Kumar, L. P. Gupta, Akanksha, R. Trivedi, H. Bid, V. L. Nayak, J. A. Siddiqui, B. Chakravarti, R. Saxena, A. Dwivedi, M. I. Siddiquee, U. Siddiqui, R. Konwar, N. Chattopadhyay, *Bioorg. Med. Chem.* **2011**, *19*, 5409-5419.

13 L. Piovan, M. F. M. Alves, L. Juliano, D. Brömme, R. L. O. R. Cunha, L. H. Andrade, *J. Braz. Chem. Soc.* **2010**, *21*, 2108-2118.

14 E. E. Alberto, V. D. Nascimento, A. L. Braga, *J. Braz. Chem. Soc.* **2010**, *21*, 2032-2041

15 a) M. Soriano-Garcia, *Curr. Med. Chem.* **2004**, *11*, 1657-1669; b) C. W. Nogueira, J. B. Rocha, *Arch. Toxicol.* **2011**, *85*, 1313-1359; c) C. Sanmartín, D. Plano, J. A.

Palop, *Mini-Rev. Med. Chem.* **2008**, *8*, 1020-1031; d) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255-6285.

16 J. Venhorst, M. Rooseboom, N. P. E. Vermeulen, J. N. M. Commandeur, *Xenobiotica* **2003**, *33*, 57-72.

17 S. Xiong, W. R. Markesbery, C. Shao, M. A. Lovell, *Antioxid Redox Signal* **2007**, *9,* 457–467.

18 a) D. Prim, J. -M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041-2075; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534-1544.

19 M. Carril, R. SanMartin, E. Domínguez, *Chem. Soc. Rec.* **2008**, *37*, 639-647.

20 M. Kosugi, T. Shimizu, T. Migita, *Chem. Lett.* **1978**, *1*, 13-14.

21 S. -I. Murahashi, M. Yamamura, K. -I. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, *44*, 2408-2417.

22 A. M. Rane, E. L. Miranda, J. A. Soderquist, *Tetrahedron Lett.* **1994**, *35*, 3225-3226.

23 G. Y. Li, *J. Org. Chem.* **2002**, *67*, 3643-3650.

24 Z. Qin, I. Kastrati, R. E. P. Chandrasena, H. Liu, P. Yao, P. A. Petukhov, J. L. Bolton, G. R. J. Thatcher, *J. Med. Chem*. **2007**, *50*, 2682–2692.

25 C. -N. Hsiao, T. Kolasa, *Tetrahedron Lett*. **1992**, *19*, 2629–2632.

26 C. S. Bryan, J. A. Braunger, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 7064–7068.

27 B. C. Ranu, K. Chattopadhyay, S. Banerjee, *J. Org. Chem.* **2006**, *71*, 423-425.

28 F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185.

29 a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; c) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, *15*, 2428-2439.

30 H. Suzuki, H. Abe, A. Osuka, *Chem. Lett.* **1980**, *9*, 1363-1364.

31 I. P. Beletskaya, A. S. Sigeev, A. S Peregudov, P. V Petrovskii, *Tetrahedron. Lett.* **2003**, *44*, 7039-7041.

32 M. S. Kabir, M. L. Van Linn, A. Monte, J. M. Cook*, Org. Lett.* **2008**, *10*, 3363-3366.

Chapter 1

1. Introduction and Objectives

33 M. S. Kabir, M. Lorenz, M. L. Van Linn, O. A. Namjoshi, S. Ara, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3626–3643.

34 a) H. Zhang, Q. Cai, D. J. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173; b) D. Ma, Q. Cai, *Org. Lett.* **2003**, *21*, 3799–3802; c) X. Xie, G. Cai, D. Ma, *Org. Lett.* **2005**, *21*, 4693–4695; d) Y. Zheng, X. Du, W. Bao, *Tetrahedron Lett.* **2006**, *47*, 1217–1220.

35 S. -R. Guo, Y. -Q. Yuan, *Synth. Commun.* **2008**, *38*, 2722–2730.

36 D. Chang, W. Bao, *Synlett* **2006**, *11*, 1786-1788.

37 Z. Wang, H. Mo, W. Bao, *Synlett* **2007**, *1*, 91-94.

38 a) I. P. Beletskaya, V. P. Ananikov, *Eur. J. Org. Chem.* **2007**, *21*, 3431-3444; b) I. P. Beletskaya, V. P. Ananikov, *Pure Appl. Chem.* **2007**, *79*, 1041-1056; c) A. Ogawa, *J. Organomet. Chem.* **2000**, *611*, 463-474.

39 a) H. Kuniyasu, A. Ogawa, K. Sato, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1992**, *114*, 5902–5903; b) H. Kuniyasu, A. Ogawa, K. -I. Sato, I. Ryu, N. Sonoda, *Tetrahedron Lett.* **1992**, *33*, 5525-5528; c) A. Ogawa, T. Ikeda, K. Kimura, T. Hirao, *J. Am. Chem. Soc.* **1999**, *121*, 5108–5114; d) I. Kamiya, E. Nishinaka, A. Ogawa, *J. Org. Chem.* **2005**, *70*, 696–698; e) V. P Ananikov, D. A Malyshev, I. P Beletskaya, G. G Aleksandrov, I. L Eremenko, *J. Organomet. Chem.* **2003,** *679*, 162-172; f) T. Ozaki, M. Kotani, H. Kusano, A. Nomoto, A. Ogawa, *J. Organomet. Chem.* **2011,** *696*, 450-455; g) T. Tamai, A. Ogawa*, J. Org. Chem.* **2014**, *79*, 5028–5035.

40 a) V. P. Ananikov, N. V. Orlov, I. P. Beletskaya, *Organometallics* **2006**, *25*, 1970–1977; b) V. P. Ananikov, N. V. Orlov, I. P. Beletskaya, *Organometallics* **2007**, *26*, 740–750; c) D. A. Malyshev, N. M. Scott, N. Marion, E. D. Stevens, V. P. Ananikov, I. P. Beletskaya, S. P. Nolan, *Organometallics* **2006**, *25*, 4462–4470; d) V. P. Ananikov, D. A. Malyshev, I. P. Beletskaya, G. G. Aleksandrov, I. L. Eremenko, *Adv. Synth. Catal.* **2005**, *347*, 1993–2001.

41 a) S. Shoai, P. Bichler, B. Kang, H. Buckley, J.A. Love, *Organometallics* **2007**, *26*, 5778–5781; b) C. Cao, L. R. Fraser, J. A. Love, *J. Am. Chem. Soc.* **2005**, *127*, 17614–17615; c) J. Yang, A. Sabarre, L. R. Fraser, B. O. Patrick, J. A. Love*, J. Org.*

Chapter 1

Chem. **2009**, *74*, 182–187; d) A. Sabarre, J. A. Love, *Org. Lett.* **2008**, *10*, 3941–3944.

42 a) L. D. Field, B. A. Messerle, K. Q. Vuong, P. Turner, *Dalton Trans.* **2009**, 3599-3614; b) S. Burling, L. D. Field, B. A. Messerle, K. Q. Vuong, P. Turner, *Dalton Trans.* **2003**, 4181-4191.

43 J. -I. Kawakami, M. Takeba, I. Kamiya, N. Sonoda, A. Ogawa, *Tetrahedron* **2003**, *59*, 6559–6567.

44 a) A. Ogawa, A. Kudo, T. Hirao, *Tetrahedron Lett.* *1998, 39*, 5213-5216; b) A. Ogawa, J. -I. Kawakami, N. Sonoda, T. Hirao, *J. Org. Chem.* **1996,** *61,* 4161-4163.

45 S. Kodama, A. Nomoto, M. Kajitani, E. Nishinaka, M. Sonoda, A. Ogawa, *J. Sulfur Chem.* **2009**, *30*, 309-318.

46 H. Kuniyasu, A. Ogawa, S. -I. Miyazaki, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1991,** *113,* 9796-9803.

47 A. Ogawa, H. Kuniyasu, N. Sonoda, T. Hirao, *J. Org. Chem.* **1997,** *62,* 8361-8365.

48 S. Higashimae, T. Tamai, A. Nomoto, A. Ogawa, *J. Org. Chem.* **2015**, *80*, 7126–7133.

49 a) H. Pellissier, *Recent developments in asymmetric organocatalysis*; Royal Society of Chemistry: Cambridge, **2010**; b) R. R. Torres, *Stereoselective organocatalysis: bond formation methodologies and activation modes*; Wiley: New Jersey, **2013**; c) C. E. Song, *Cinchona alkaloids in synthesis and catalysis: ligands, immobilization and organocatalysis*, Wiley-VCH: Weinheim, **2009**; d) G. Zhan, W. Dua, Y. -C. Chen, *Chem. Soc. Rev.* **2017,** *46,* 1675-1692; e) T. Govender, P. I. Arvidsson, G. E. M. Maguire, H. G. Kruger, T. Naicker, *Chem. Rev.* **2016**, *116*, 9375–9437; f) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431; g) C. M. Marson, *Chem. Soc. Rev.* **2012,** *41*, 7712-7722.

50 a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167-178; b) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138-1167; c) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774-793.

51 P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807–8864.

52 L. F. Casona, C. C. Wanser, *J. Am. Chem. Soc.* **1951**, *73*, 142–145.

1. Introduction and Objectives

53   M. Ménanda, V. Dalla, *Synlett* **2005**, *1*, 95-98.

54   P. Kotrusz, Š. Toma, *Molecules* **2006**, *11*, 197-205.

55   a) T. E. Kristensen, T. Hansen, *Eur. J. Org. Chem.* **2010**, *17*,3179– 3204; b) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815–838. c) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis, M. J. Vicent, J. A. Mayoral, *React. & Funct. Polym.* **2001**, *48*, 25–35; d) N. Madhavan, C. W. Jones, M. Weck, *Acc. Chem. Res.* **2008**, *41*, 1153–1165; e) C. Aranda, A. Cornejo, J. M. Fraile, E. García-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martinez-Merino, Z. Ochoa, *Green Chem.* **2011**, *13*, 983–990.

56   S. Bonollo, D. Lanari, J. M. Longo, L. Vaccaro, *Green Chem.* **2012**, *14*, 164–169.

57   Y. -T Dong, Q. Jin, L. Zhou, J. Chen, *Org. Lett.* **2016**, *18*, 5708-5711.

58   J. Wang, H. Li, Y. Mei, B. Lou, D. Xu, D. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678-5687.

59   S. A. Westcott, J. D. Webb, D. I. McIsaac, C. M. Vogels, WO2006/089402 A1, **2006**.

60   J. A. Fernández-Salas, S. Manzini, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5829-5831.

61   F. J. Lawlor, N. C. Norman, N. L. Pickett, E. G. Robins, P. Nguyen, G. Lesley, T. B. Marder, J. A. Ashmore, J. C. Green, *Inorg. Chem.* **1998**, *37*, 5282-5288.

62   W. R. Leonard, T. Livinghouse, *J. Org. Chem.* **1985**, *50*, 730–732.

63   T. Ishiyama, K. -I. Nishijima, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, *115*, 7219-7225.

64   Q. Cui, D. G. Musaev, K. Morokuma, *Organometallics* **1998**, *17*, 1383-1392.

"Leave it better than you found it."

Sir. Robert Baden-Powell

Chapter 2

1,4-Addition of pinB-SR to activated olefins

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

2.1. Introduction

2.1.1. Sulfa Michael Addition (SMA)

The synthesis of β-sulfido carbonyl compounds and related compounds has principally been covered by the conjugate addition of thiols to α,β-unsaturated carbonyl compounds.[1] Due to the importance of the C-S bond in biosynthetic processes and organic synthesis, a large number of methods have been reported for the 1,4-addition of thiols to electron-deficient olefins. However, catalytic approaches are required to activate both the substrate and the reagent to promote the formation of C_β-S bond in a precise way.[2]

In 2002 professor M. Zahouily and co-workers used $Na_2CaP_2O_7$ as an heterogeneous catalyst for the Michael addition of mercaptanes to chalcone derivatives, with high yields, in few minutes (96% yield in 5 min) and mild reaction conditions (Scheme 2.1).[3] With this catalyst, the basic sites (oxygens of $P_2O_7^{4-}$ group) abstract the proton from the thiols and the acidic sites (phosphorus of $P_2O_7^{4-}$ group, Na^+ and Ca^{2+} cations) induced the polarization of the C=O bond for the Sulfa Michael addition.

R = Ph, o-NH$_2$-C$_6$H$_4$, CH$_2$CO$_2$Et
R' = H, m-NO$_2$, p-Cl
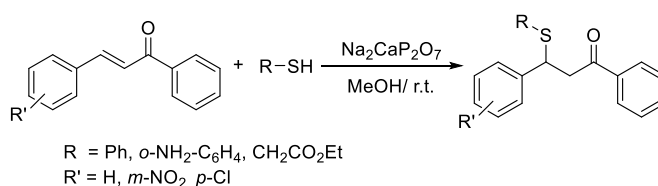
Scheme 2.1 Heterogeneous catalyst for sulfa Michael addition.

Another interesting approach of catalytic sulfa Michael addition is the one reported by M. Shibasaki *et al.*[4] They reported a heterobimetallic asymmetric complex, LaNa$_3$-tris(binaphthoxide) (LSB), as a very useful catalyst for the addition of thiols to cycloalkenones. Under these reaction conditions they afforded β-sulfonated compounds with yields up to 93% and enantioselectivity up to 84% e.e. in 20 min.

2. 1,4-Addition of pinB-SR to activated olefins

The LSB is a multifunctional asymmetric catalyst in which the sodium naphthoxide moiety might function as a Brønsted base to activate the thiol, and the metal center (La) should function as a Lewis acid to activate the cycloalkenone, thereby making possible an effective catalytic asymmetric Michael addition of a thiol to a cycloalkenone (Scheme 2.2).
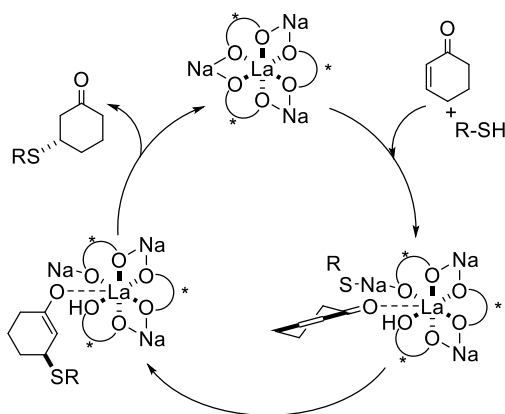
Scheme 2.2 Proposed catalytic cycle for the catalytic Michael addition of thiols to cycloalkenones.

The asymmetric induction of the sulfa Michael addition has been deeply studied from the organocatalytic point of view, through cinchona alkaloid derivatives as the most used.[5]

Pioneering studies on the asymmetric 1,4-addition of thiols promoted by chiral cyclic amines as catalysts, chinchonidine and proline, were done by the group of Wynberg[6] and the group of Mukaiyama,[7] respectively. They reported that a hydroxy group in the β-position respect the amino group was necessary for the reaction to take place. They reported a bifunctional mechanism involving the simultaneous activation of the cyclic enone and the thiol by the hydroxy and the amino groups, respectively (Figure 2.1).
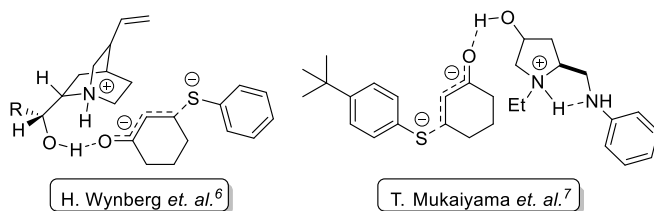
Figure 2.1 Proposed transition states for the bifunctional mechanism involving chinchonidine and proline catalysts.

Despite the mild nucleophilicity of the sulphur moiety in thiol reagents,[8] the reaction conditions frequently favored the formation of byproducts from side reactions such as self-condensation, polymerization or rearrangements.[9]

Pointing at the nature of the sulphur reagent, we focused our attention to thiodioxaborolanes, pinB-SPh (**1**), pinB-STol (**2**) and pinB-SBn (**3**) (Figure 2.2), since they are easy to prepare and the "*pull-push*" effect of the boryl unit might enhance the nucleophilic character of the interelement. In the following section the relevant properties of this type of reagent will be discussed.

pinB-SPh **1**   pinB-STol **2**   pinB-SBn **3**
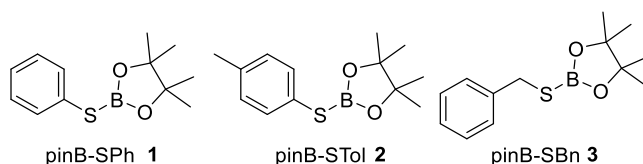
Figure 2.2 Structure of thiodioxaborolanes.

2.1.2. Properties of the Thiodioxaborolanes

Thiodioxaborolanes are a family of compounds constituted by a boron atom substituted by two oxygens and one sulphur atom. The pinacolboryl is one of the most stable moieties in dioxaborolanes, because the oxygens mitigate the Lewis acidic properties of the boron atom.

2. 1,4-Addition of pinB-SR to activated olefins

An interesting property of trivalent boron compounds is the "*pull-push*" effect. This effect consists in a quaternization of the boryl unit that might enhance the nucleophilic character of the interelement bonded to it.[10]

Despite the fact that boron reagents have principally been activated by transition metal complexes[11], a current trend has shown the easy and convenient activation of diboron reagents by Lewis bases, such as N-heterocyclic carbenes (NHCs).[12] Even more interesting, alkoxides can interact with diboranes, silaboranes and aminoboranes by forming the corresponding Lewis acid–base adducts [Nu→B(OR)$_2$–B(OR)$_2$],[13] [Nu→B(OR)$_2$–SiMe$_2$Ph][14] and [Nu→B(OR)$_2$–NR'$_2$],[15] facilitates the release of a boryl, silyl or amine moiety with enhanced nucleophilic character (Scheme 2.3). Another related example, reported recently, involves the activation of an heterodiboron pinB-Bdan (dan = 1,8-diaminonaphthalene) by alkoxides to selectively transfer the Bdan fragment to α,β-unsaturated substrates (Scheme 2.3).[16]
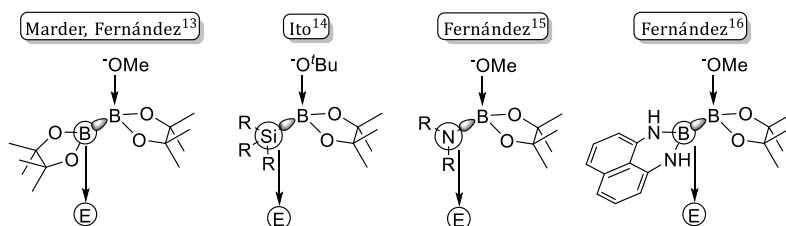
Scheme 2.3 Illustrative pictures of the Lewis acid-base adducts. E= electrophilic reagent.

More recently, in the. Fernández's research group, it has been able to observe that pinB-SePh (**4**) reagent can also be activated by Lewis bases, but the most remarkable circumstance is that the electron rich C=O of α,β-unsaturated ketones and aldehydes can activate the phenylselenium borane reagent, without the need of external Lewis bases or additives. This face to face reactivity is unusual and theoretical calculations have demonstrated that this activation is more likely in B-E when E=Se > S > O.[17]

40

2.1.3. Reaction pathway for selenoboration

In the previous work done in the laboratory with pinB-SePh (**4**)[17] a possible reaction pathway was proposed by Dr. C. Bo and Dr. X. Sanz throughout theoretical calculations. In the Figure 2.3 the reaction pathway for the reaction of **4** with 3-penten-2-one is shown.
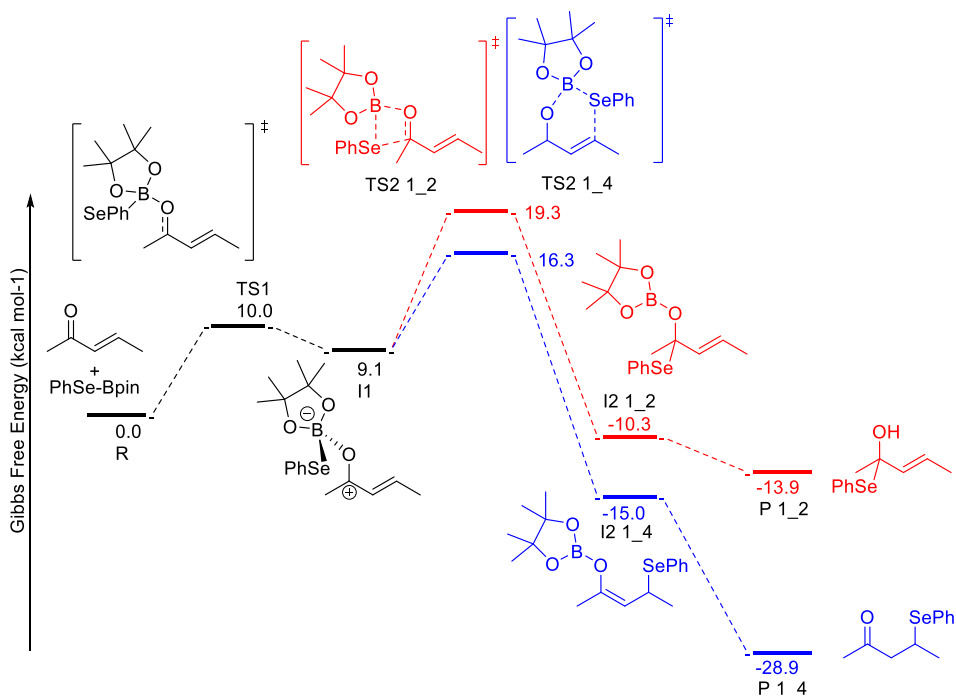
Figure 2.3 Proposed reaction pathway by Sanz/Bo.[17] All energies are in kcal·mol⁻¹.

In the first step, the carboxylic 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**) which lies 9.1 kcal·mol⁻¹ above the reactants. 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 (**TS2 1_4**) or the carboxylic carbon (**TS2 1_2**).

2. 1,4-Addition of pinB-SR to activated olefins

It is important to highlight that the 1,4-addition pathway is less energetically demanding than the 1,2-addition, and also it leads to a more stable intermediate **I2 1_4**, which after a work-up becomes the most stable β-selenated ketone (**P 1_4**). Therefore, the 1,4-addition product **P 1_4** is obtained from both kinetic and thermodynamic reasons.

In the same study, some calculations of a similar reaction between pinB-SPh (**1**) and 3-penten-2-one were carried out, predicting the favorable outcome of the SPh addition on the C_β. Then thioboration of 4-hexen-3-one with **1** (Scheme 5), was carried out, as part of a preliminary study.[17]

Conversion 93%
Isolated Yield 58%
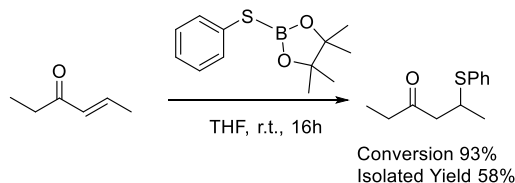
Scheme 2.4 Reactivity of pinB-SPh to 4-hexen-3-one.

2.2. Motivation

Since the previously reported synthesis of organosulfides required the presence of a catalyst to work; and based on the previous work done in our group about the activation of pinB-SePh with α,β-unsaturated carbonyl compounds, we became determined to demonstrate the activation of pinB-SPh (**1**), pinB-STol (**2**) and pinB-SBn (**3**) by α,β-unsaturated ketones and aldehydes and provide an alternative sulfa Michael addition, that does not need catalysts or drastic reactions conditions to generate a new C_β-S bond (Scheme 2.5).
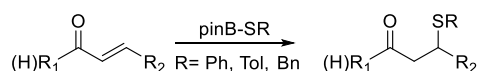
Scheme 2.5 Expected reactivity of the vinyl carbonyl compounds with B-S reagents.

42

2.3. Results and discussion

With the aim of activating pinB-SPh (**1**) and selectively transfer the PhS moiety to activated olefins, we first attempted the conjugate addition on 4-phenyl-3-buten-2-one (**5**) as a model substrate. The starting conditions were the same as the ones used by Fernandez *et al.*[17] for the synthesis of *β*-(phenylselenium) substituted ketones and aldehydes. Therefore, we have adapted for the thioboration the use of 1.1 equiv. of **1** in 2 mL of dry THF at room temperature, working in 0.1mmol scale of substrate (Scheme 2.6).
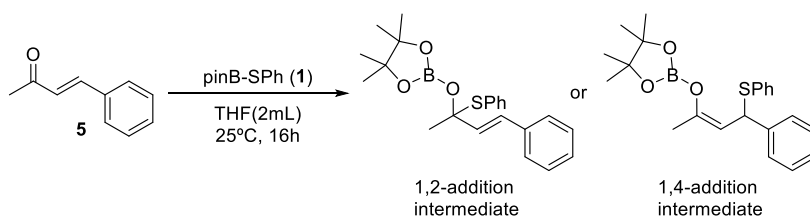
Scheme 2.6 Reactivity of pinB-SPh (**1**) with 4-phenyl-3-buten-2-one (**5**).

When the reaction was carried out under these reaction conditions, low percentages of *β*-(phenylthio) substituted ketone, (< 5% of conversion), was observed. An excess of pinB-SPh (4.5 equiv.) increased the conversion up to 98% but we did not observe the expected *β*-sulfido ketone product. Instead, the ^{1}H NMR showed two interesting doublets that integrate one proton each between 5.0 and 5.5 ppm, and a singlet around 2 ppm that integrates three protons (Figure 2.4). Moreover, in the ^{13}C NMR spectra we were aware that no signal for the carbonyl carbon (about 200 ppm) was observed. After that observation and according to these NMR results, two possible structures could match with these signals. One possibility was the 1,2-addition intermediate and the other was the 1,4-addition intermediate.

2. 1,4-Addition of pinB-SR to activated olefins
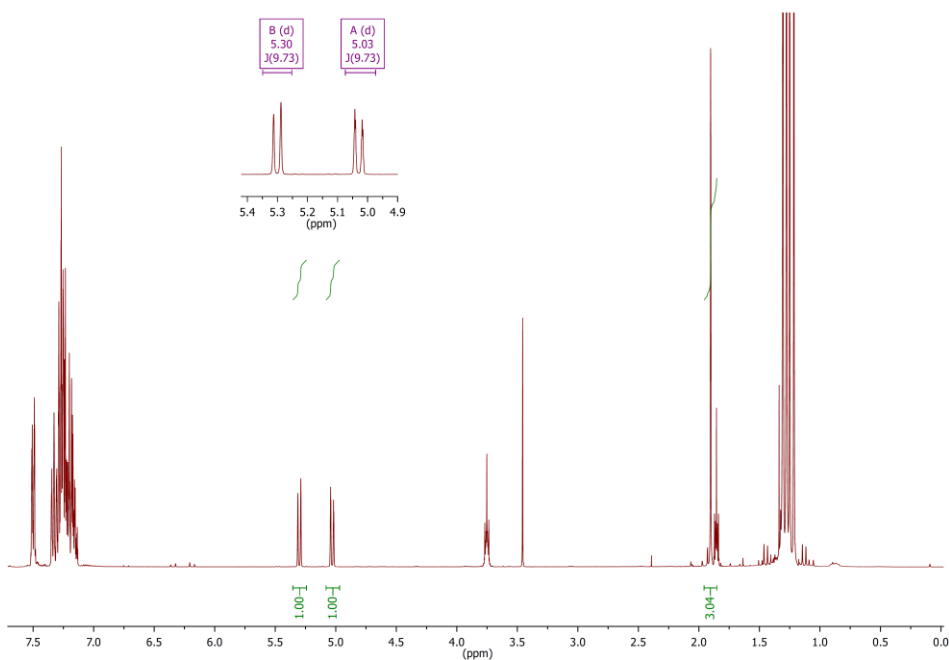
Figure 2.4 ^{1}H NMR of the crude of the thioboration of 4-phenyl-3-buten-2-one (**5**)

When we conducted the same reaction with other substrate that contain aryl groups in C_β, it was possible to observe a similar set of NMR spectra (^{1}H and ^{13}C NMR). Therefore 4-(4-methoxyphenyl)-3-buten-2-one (**6**), 4-(4-chlorophenyl)-3-buten-2-one (**7**) and *trans*-chalcone (**8**), were quantitatively transformed into the same thioborated products in an exclusive way.

Looking at the coupling constants of the two doublets in Figure 2.4 (between 5.0 – 5.5 ppm), the average value was 9.7 Hz. If it is considered that the vinylic coupling constant in the 1,2-addition intermediate has a value between 11–18 Hz and the allylic coupling constant in the 1,4-addition intermediate should be about 4–10 Hz, it can be assumed that our coupling constant fits better with the second type of compounds.

To complete the characterization of the thioborated product, we carried out a bidimensional NMR experiment, HSQC 2D. The study was carried out at the crude of the thioboration reaction of the *trans*-chalcone (**8**).

44
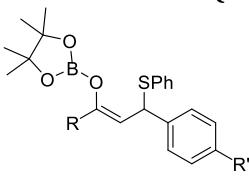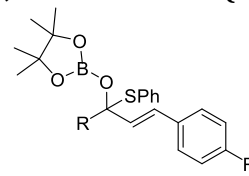
Figure 2.5 shows the correlation between H and C. Significantly, the doublet at 5.4 ppm is correlated with a carbon at about 50 ppm, while the doublet about at 5.8 ppm is correlated with a C at 110 ppm, approximately. This agrees with the fact that each doublet belongs to a C sp^3 and C sp^2 respectively, and it is more related to the 1,4-addition intermediate (**8b**).
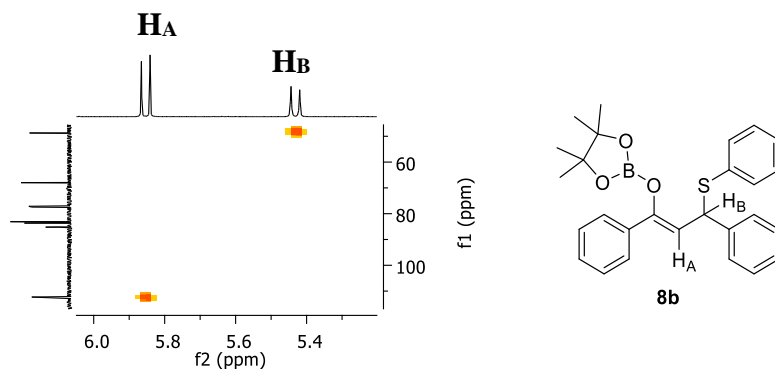
Figure 2.5 Enlargement of HSQC 2D of the *trans*-chalcone's reaction crude

Once the thioborated intermediate was identified, we could quantify the reaction out come in the four thioboration reactions carried out so far. Table 2.1 shows quantitative conversion without any byproduct formation of substrates **5-8** into the 1,4-addition intermediate.

Table 2.1 Thioboration of α,β-unsaturated ketones with aryl groups in C$_\beta$ [a]

Entry	Substrate			Conv. (%)	1,4-intermediate (%)[b]	1,2-intermediate (%)[b]
	R	R'				
1	Me	H	**5**	98	99 **5b**	---
2	Me	OMe	**6**	99	99 **6b**	---
3	Me	Cl	**7**	99	99 **7b**	---
4	Ph	H	**8**	97	99 **8b**	---

[a] The thioboration was carried out with substrate (0.10 mmol), pinB-SPh (4.5 equiv.), THF (2 mL), 25 °C, 16 h. [b] Calculated by NMR spectroscopy from an average of two essays.

2. 1,4-Addition of pinB-SR to activated olefins

Next, we conducted the thioboration of cyclic α,β-unsaturated ketones, as well as α,β-unsaturated aldehydes to study the thioborated products. Therefore, the 2-cyclohexenone (**9**) and crotonaldehyde (**10**) were reacted with 4.5 equiv. of pinB-SPh (**1**), at room temperature for 16 h. The ^{1}H NMR spectra of the 2-cyclohexanones's crude reaction shows two different groups of signals in 73/27 ratio. The major signals are two double triplets at 5.95 ppm and 5.75 ppm that were correlated with two carbons at 125 ppm (Figure 2.6), in agreement with the formation of the 1,2-addition intermediate (**9a**).
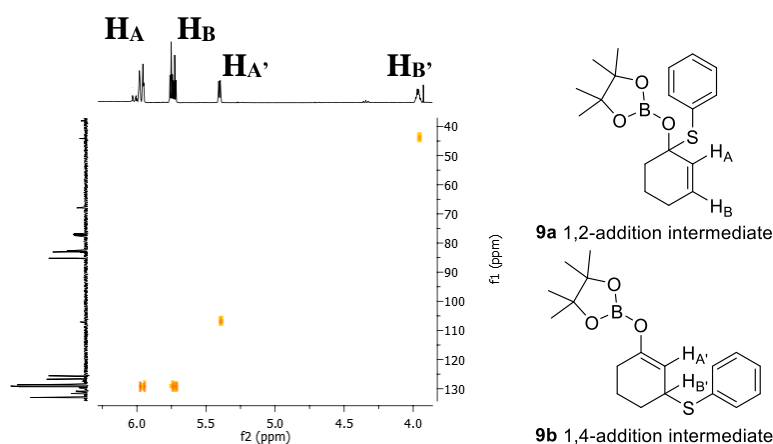
Figure 2.6 Enlargement of HSQC 2D NMR of crude reaction of thioboration of **9**.

The minor signals that appeared at 5.4 ppm and 3.9 ppm, in the ^{1}H NMR, were correlated with an allylic and vinylic carbon, respectively (Figure 2.6) in the HSQC 2D NMR experiment. These data agreed with the minor formation of the 1,4-addition intermediate (**9b**).

The major presence of the 1,2-addition intermediate can be explained by the mechanism of the reaction. In the case of the cyclic substrates, were the C=O and C=C are in *trans,* the activation of the boron atom and the delivery of the SPh group to the β carbon seems to be more geometrically restricted than the addition to the carboxylic carbon.

Interestingly, when the thioboration of the α,β-unsaturated aldehyde crotonaldehyde (**10**) was performed under the same reaction conditions, the unique thioborated intermediate observed was the 1,2-thioborated isomer (**10a**) (Figure 2.7). The signals appeared at 5.8 and 5.6 ppm correlated with two carbons at about 128 ppm, and the doublet at 5.9 ppm correlates with the carbon at 83 ppm, supporting that the aldehyde functional group has been transformed into –CH(OBpin)(SPh). In this case, because the aldehyde is more reactive than a ketone, the only intermediate observed is the 1,2.
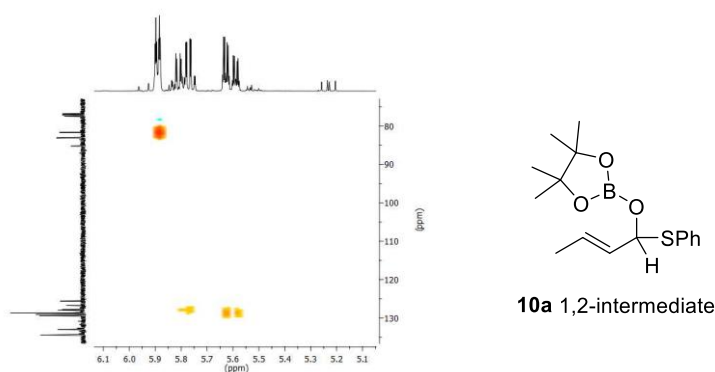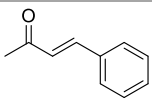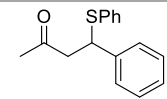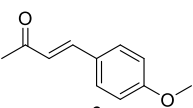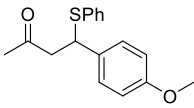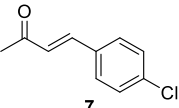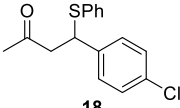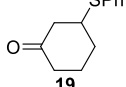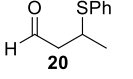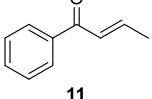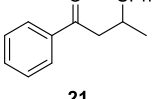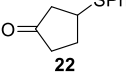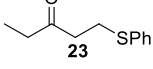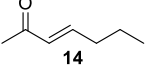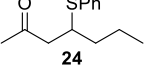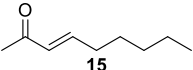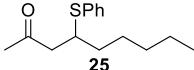

Figure 2.7 Enlargement of HSQC 2D of **10b** in the reaction crude.

After quantitative conversion of substrates **5,6,7,9,10** into thioborated products, the protic work up carried out with addition of MeOH (2 mL) provided the corresponding β-sulfido carbonyl compounds **16** to **20** (Table 2.2, entries 1–5). A plausible rearrangement of 1,2-thioborated intermediates **9a** and **10a** toward the β-sulfido carbonyl compounds seems to occur under the *in situ* protic work up.[18] In order to discard the possible *in situ* formation of PhSH and consequently the direct interaction with the α,β-unsaturated carbonyl substrates, we ran the same reaction as in Table 2.2, entry 5, using PhSH instead of pinB-SPh (**1**). As was it expected, there was no β-sulfido cyclohexanone formation due to the lack of catalytic activation of the thiol.

47

2. 1,4-Addition of pinB-SR to activated olefins

The substrate *trans*-1-phenyl-2-buten-1-one (**11**) was more efficiently converted into the corresponding product **21** (Table 2.2, entry 6) than the analogue 4-phenyl-3-buten-2-one (**5**) (Table 2.2, entry 1) which required 4.5 equiv. of pinB-SPh (**1**) for similar conversion. The Ph substituent bonded to the C=O on the ketone **11** seems to facilitate the interaction of the lone pair from C=O to Bpin and for that reason substrate **11** needs 3 equiv. of **1**.

Table 2.2 Thioboration/protonation of electron deficient ketones [a]

Entry	Substrate	Product	Conv. (%)[b]	[I.Y.] (%)
1	**5**	**16**	76	64
2	**6**	**17**	78	70
3	**7**	**18**	87	75
4	**9**	**19**	78	70
5	**10**	**20**	87	80
6[d]	**11**	**21**	88	72
7	**12**	**22**	82	78
8[c]	**13**	**23**	99	81
9[d]	**14**	**24**	99	80
10[d]	**15**	**25**	91	71

[a] Reaction conditions: Substrate (0.1 mmol), pinB-SPh (4.5 equiv.), THF (2 mL), 25 °C, 16 h/Addition MeOH (2 mL), 2 h. [b] Conversion calculated from an average of two assays. [c] pinB-SPh (1.1 equiv.). [d] pinB-SPh (3 equiv.).

The cyclic *α,β*-unsaturated ketone 2-cyclopente-1-one (**12**) was also efficiently transformed into the *β*-(phenylthio)-cyclopentanone (**22**) in a 78% I.Y. (Table 2.2, entry 7). The thioboration of the aliphatic non-cyclic *α,β*-unsaturated substrates 1-penten-3-one (**13**), 3-hepten-2-one (**14**), and 3-nonene-2-one (**15**) required less amount of the pinB-SPh reagent (1.1–3 equiv.) to obtain quantitative conversion into the *β*-sulfido carbonyl compounds **23**, **24**, and **25** (Table 2.2, entries 8–10).

When the thioboration of **14** was carried out in MeOH, as the unique solvent, quantitative formation of the desired *β*-sulfido ketone was observed within 6 h. We have noticed, in that case, that the use of MeOH as solvent reduces the reaction time.

After the study of the scope of the thioboration with pinB-SPh (**1**), we decided to analyze the thiodioxaborolanes pinB-STol (**2**) and pinB-SBn (**3**). Selecting 3-nonene-2-one (**15**) and 4-hexen-3-one (**26**) as the Michael acceptors, we conducted the thioboration/protonation within 16 h at room temperature. The formation of the corresponding *β*-sulfido carbonyl compounds containing TolS results in 61% and 75% I.Y. for **29** and **31,** respectively. The ones containing the BnS were isolated up to 55% for **27** and 30% for **30** (Figure 2.8).
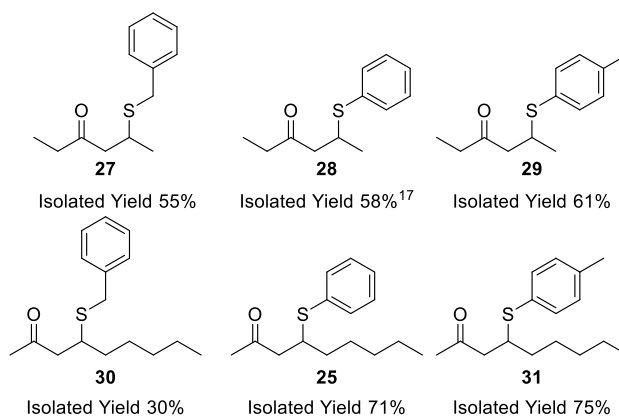

Figure 2.8 Comparative study of reactivity with thiodioxaborolonaes.

2. 1,4-Addition of pinB-SR to activated olefins

This experimental work was complemented by means of DFT calculations. The theoretical approach was carried out by my co-worker Xavi Sanz and the results are here summarized to complement the experimental results.

It was calculated the reaction pathway for the 1,4-addition and 1,2-addition of pinB-SPh (**1**) to 4-phenyl-3-buten-2-one (**5**). All the activation free energies for the 1,2-addition pathway are higher than the corresponding ones for the 1,4-addition pathway. Also, the intermediate for the 1,2-addition is less stable than the corresponding for the 1,4-addition and the formation of the 1,2-addition product is less favored than the formation of the 1,4-addition ones (Figure 2.9).
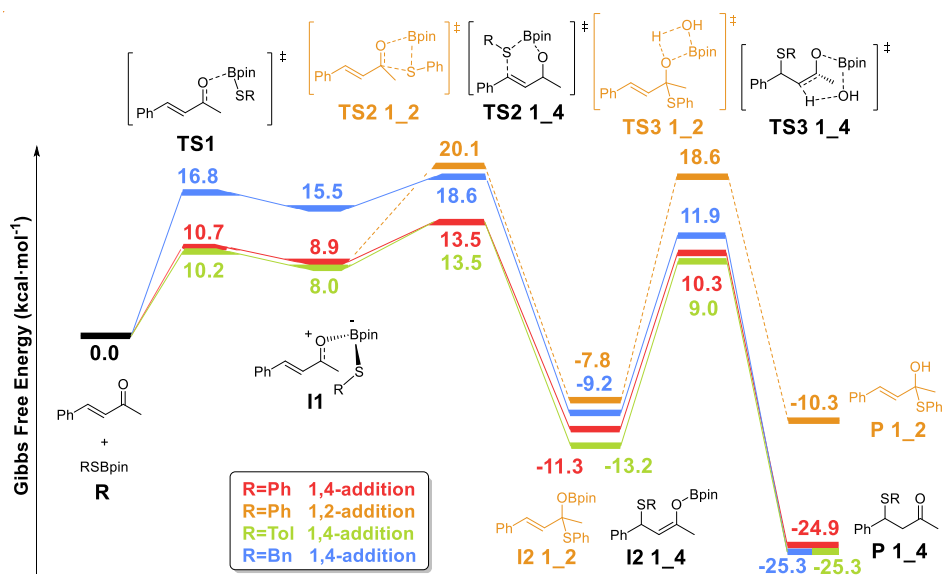
Figure 2.9. Calculations carried out by X. Sanz under the supervision of Dr. Bo.

In the reaction pathway for the thioboration reaction of substrate 2-cyclohexenone (**9**) with **1** was found that it follows a 1,2-addition pathway. However, 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.

50

However, when water or methanol were involved in the calculation as protonation agents, the models evolved directly to the formation of the final 1,4-product and pinB-OH (or pinB-OMe). Thus, it is suggested that the interconversion from 1,2- to 1,4-addition intermediates does not take place directly but 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.

The difference of reactivity between pinB-SPh (**1**), pinB-STol (**2**) and pinB-SBn (**3**) was justified through two different calculations. First a nucleophilic indexes (N) were calculated showing the following trend: the pinB-STol (**2**) is the better nucleophile with a N of 3.35 eV, followed by pinB-SPh (**1**) (N = 3.24 eV) and finally the pinB-SBn (**3**) with 2.89 eV of N.

The observed theoretical trend is in agreement with our experimental data because, the reaction pathway shows that the thiodioxaborolane pinB-SBn (**3**) is less reactive than the other two reagents by the fact that higher activation energies are observed in the reaction pathways. It's worthy to mention that the computed values for the pinB-STol and pinB-SPh reactions are very similar, being the pinB-STol slightly more reactive, as it was also demonstrated experimentally.

2.4. Conclusions

The synthesis of β-sulfido carbonyl compounds can be achieved through a direct thioboration/protonation between activated olefins and thiodioxaborolanes. The PhS, TolS, and BnS moieties can be delivered from the thiodioxaborolanes pinB-SPh (**1**), pinB-STol (**2**), and pinB-SBn (**3**) by the simple activation of the Bpin moiety with a carbonyl group. This strategy is performed at room temperature in the absence of any catalyst, additive or base. The thioboration generates 1,4-addition as well as 1,2-addition intermediates, depending on the structural nature of the substrate.

Protic workup delivers the corresponding β-sulfido carbonyl compounds in moderate to good isolated yields. From the thiodioxaborolanes studied, the pinB-SBn (**3**) is less reactive presumably because of the lack of electron delocalization from sulfur, making the boron atom less Lewis acidic

2.5. References

1   a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Oxford: Pergamon Press, **1992**; b) D. Enders, K. Lüttgen, A. A. Narine, *Synthesis*, **2007**, *7*, 959-980.

2   a) N. K. Rana, S. Selvakumar, V. K. Singh, *J. Org. Chem.*, **2010**, *75*, 2089-2091; b) J. S. Yadav, B. V. S. Reddy, G. Baishya, *J. Org. Chem.*, **2003**, *68*, 7098-7100; c) H. Zhang, Y. Zhang, L. Liu, H. Xu, Y. Wang, *Synthesis*, **2005**, *13*, 2129-2136; d) Y. Zhao, Z.-M. Ge, T. -M. Cheng, R. -T. Li, *Synlett*, **2007**, *10*, 1529-1532; e) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi, E. Torregiani, *J. Org. Chem.*, **2005**, *70*, 169-174; f) B. M. Trost, D. E. Keeley *J. Org. Chem.* **1975**, *40*, 2013;

3   M. Zahouily; Y. Abrouki, A. Rayadh, *Tetrahedron Lett.* **2002**, *43*, 7729-7730.

4   E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 4043.

5   a) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 17934–17941; b) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49–53; c) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7892–7894.

6   a) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87-129; b) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417-430.

7   K. Suzuki, A. Ikegawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277-3282.

8   a) T. Kondo, T. A. Mitsudo, *Chem. Rev.*, **2000**, *100*, 3205-3220; b) M. Sibi, S. Manyem, *Tetrahedron*, **2000**, *56*, 8033-8061.

9   L. Novak, P. Kolontis, C. Szantay, D. Aszodi, M. Kajtar, *Tetrahedron* **1982**, *38*, 153-159.

10   a) J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.*, **2012**, *41*, 3558-3570; b) J. Cid, J. J. Carbó, E. Fernández, *Chem. Eur. J.* **2012**, *18*, 12794-12802; c) A. B. Cuenca, R. Shishido, H. Ito, E. Fernández, *Chem. Soc. Rev.* **2017**, *46*, 415-430; d) R. D. Dewhurst, E. C. Neeve, H. Braunschweig, T. B. Marder, *Chem. Commun.* **2015**, *51*, 9594-9607; e) S. Pietsch, E. C. Neeve, D. C. Apperley, R.

Chapter 2

53

2. 1,4-Addition of pinB-SR to activated olefins

Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radius, Z. Lin, C. Kleeberg, T. B. Marder, *Chem. Eur.J.* **2015**, *21*,7082 –7099.

11 a) S. A. Westcott, E. Fernández, *Adv. Organomet. Chem.* **2015**, *63,* 39-89; b) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091–9161.

12 a) K. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255; b) M. Gao, S. B. Thorpe, C. Kleeberg, C. Slebodnick, T. B. Marder, W. L. Santos, *J. Org. Chem.* **2011**, *76*, 3997–4007.

13 a) A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.* **2010**, *49*, 5130-51354; b) A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.* **2011**, *50*, 7158-7161; c) C. Sole, H. Gulyás, E. Fernández*, Chem. Commun.* **2012**, *48*, 3769-3771; d) A. Bonet, C. Solé, H. Gulyás and E. Fernández, *Org. Biomol. Chem.* **2012**, *10*, 6621-6623.

14 a) J.M. O'Brien, A.H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712-7715; b) K. Oshima, T. Ohmura, M. Suginome, *Chem. Commun.* **2012**, *48*, 8571-8573; c) H. Ito, Y. Horita, E. Yamamoto, *Chem. Commun.* **2012**, *48*, 8006-8008.

15 C. Solé, E. Fernández*, Angew. Chem. Int. Ed.* **2013**, *52*, 11351-11355.

16 J. Cid, J. J. Carbó, E. Fernández, *Chem. Eur. J.* **2014**, *20*, 3616–3620.

17   X. Sanz, C. M. Vogels, A. Decken, C. Bo, S. A. Westcott, E. Fernández*, Chem. Commun.* **2014**, *50*, 8420-8423.

18 S. K. Bur, *Top. Curr. Chem.*, **2007**, *274*, 125-171.

"A Scout smiles and whistles under all circumstances."

Sir. Robert Baden-Powell

Chapter 3

1,4-Addition of pinB-SR and pinB-SeR to ynones

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

3.1. Introduction

Vinyl chalcogenides[1] such as vinyl selenides and vinyl sulfides are compound of great interest in organic synthesis due to their wide applicability in reactions such as cross coupling (Scheme 3.1),[2] sigmatropic rearrangements,[3] Diels-Alder reactions[4] among many other reactions. These compounds have also shown antioxidant properties.[5]
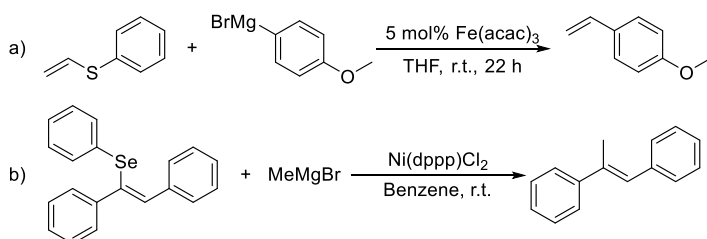
Scheme 3.1. a) Iron- and b) Nickel-catalyzed cross coupling of vinyl chalcogenides with Grignard reagents.

The synthesis of vinyl chalcogenides 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]

The synthesis of vinyl selenides and vinyl sulfides in a metal free context using B-S or B-Se reagents, has been limited to the reaction of organoselenoboranes with acetylenes by a free radical 1,2-addition (Scheme 3.2).[7]
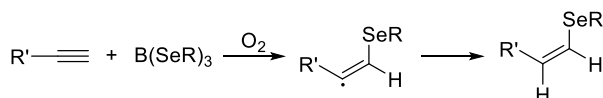
Scheme 3.2. Synthesis of vinyl selenides throughout organoselenoboranes.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

Alternatively, the synthesis of β-seleno and β-sulfido vinyl carbonyl compounds has been addressed with relative success. The first synthesis of β-sulfido vinyl carbonyl compounds was reported in 1982 by Omote *et. al.*[8] They studied the reaction of 3-(1-imidazolyl)-2-alken-1-ones with thiophenol (Scheme 3.3). This reaction is based in a substitution, where the deprotonated PhS⁻ substitutes the imidazolyl group.
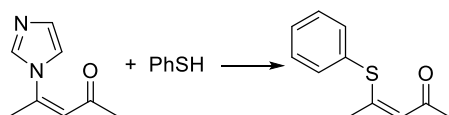
Scheme 3.3. Addition of thiophenol to 3-(1-imidazolyl)-2-alken-1-ones.

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.[9] Later in 1998 Meng and co-workers introduced the first selenocarbonylation addition reaction of selenoesters to nonactivated terminal alkynes under the catalysis of CuX species. The reaction provided the (*Z*)-β-arylseleno-α,β-unsaturated ketones in high yields and selectivity values (Scheme 3.4).[10]
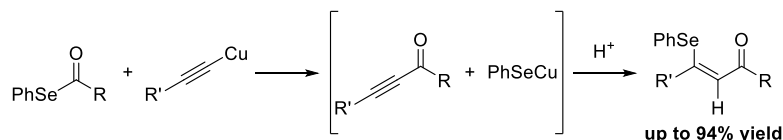
Scheme 3.4. Selenocarbonylation of selenoesters to nonactivated alkynes.

More recently a four-component coupling reaction to yield (*Z*)-β-selenyl acrylamides has been reported by Meyer and co-workers. The reaction takes place with regio- and stereoselectively and it is catalyzed by Pd(PPh$_3$)$_4$ after mixing sulfenamide, alkyne, carbon monoxide, and diphenyl diselenide in one-pot protocol.

The products are obtained in good to excellent yields (60-95%) and the reaction tolerates a range of functional groups on the nitrogen of the sulfenamide and the alkyne (Scheme 3.5).[11]
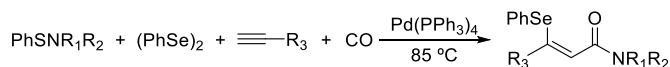
Scheme 3.5 Palladium-catalyzed synthesis of β-selenyl acrylamides.

In 2008 Kuniyasu and Kambe reported the Pt-catalyzed decarbonylative arylthiolation by thioesters of unsymmetrical internal alkynes. This reaction takes place with 8 mol% of $Pt(PPh_3)_4$ in xylene at 140 °C during 48 hours. When they used ethyl phenylpropiolate as substrate, it was obtained the *E*-phenylthio tetrasubstituted alkene with regio- and stereoselective control (Scheme 3.6).[12]
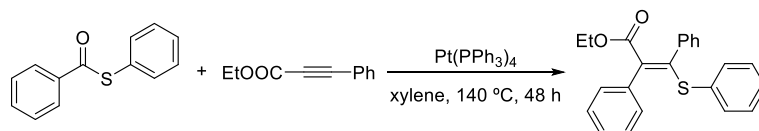
Scheme 3.6. Platinum-catalyzed arylthiolation of ethyl phenylpropiolate.

At the same time, the synthesis of these compounds has been achieved throughout a clean and efficient solvent-free protocol for hydrochalcogenation of propargylic esters, ketones and nitriles. It has been used phenylchalcogenolate anions generated *in situ* from the respective diphenyl dichalcogenide (Se, Te, S), using alumina supported sodium borohydride. This method provided the (*Z*)-β-phenylchalcogeno-α,β-unsaturated products in good yields (Scheme 3.7).[13]
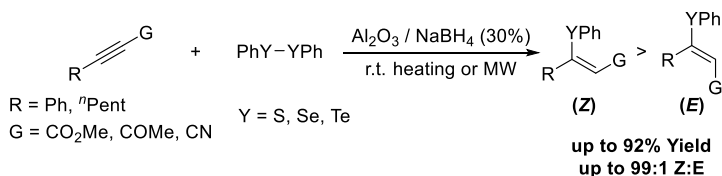
Scheme 3.7. Hydrochalcogenation of propargylic esters, ketones and nitriles.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

Also in 2007, Comasseto and co-workers reported the reaction of enol phosphates of *β*-dicarbonyl compounds with lithium organoselenolates to give (*Z*)-*β*-organoseleno-*α*,*β*-unsaturated carbonyl compounds (Scheme 3.8).[14]
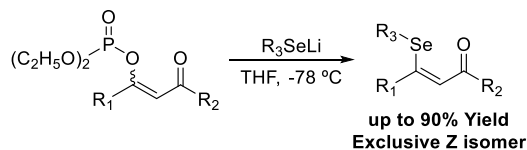
Scheme 3.8. Reaction of enol phosphates with lithium organoselenolates.

Later on, in 2009, the synthesis of *Z*-arylthio acrylates was achieved by Rao and co-workers using CuO nanoparticles. The cross-coupling reaction of *Z*-ethyl-3-iodoacrylate with different aryl thiol in DMSO at 80 °C afforded the desired products in high isolated yields and with retention of stereochemistry (Scheme 3.9). Under these conditions no ligand is needed to proceed and this methodology was proved to be useful with a wild variety of vinyl halides.[15]
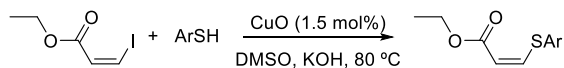
Scheme 3.9. Nano CuO-catalyzed cross-coupling of 3-haloacrylate with aryl thiols.

In 2011, Santi and co-workers reported the Michael addition of the reagent PhSe-ZnCl to electron-deficient alkynes, leading to synthetically useful vinyl selenides. The reaction was performed at room temperature in THF or water and the reaction showed to be very selective towards the *Z* isomer (Scheme 3.10).[16]
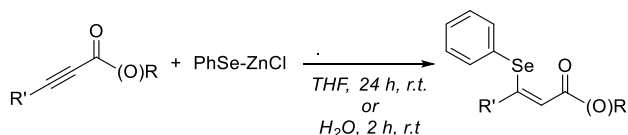
Scheme 3.10. Michael addition of PhSe-ZnCl to propargylic ketones and esters.

60

3.2. Motivation

Bearing in mind that synthesis of vinyl selenides and vinyl sulfides conjugated to carbonyl groups is not a deeply explored field and that mostly of the previous reported synthesis required metal catalyst and/or suffer from low yields, we became interested to efficiently promote the synthesis of vinyl selenides and vinyl sulfides in the absence of transition metal complexes or additives. To do so, we used the reagents pinB-SPh (**1**), pinB-SBn (**3**) and pinB-SePh (**4**) to be added to activated alkynes (Scheme 3.11).
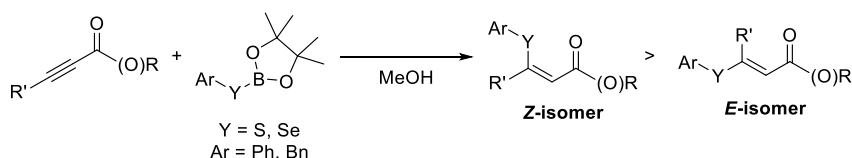
Scheme 3.11. Synthesis of vinyl chalcogenides throughout chalcogenoborates.

3.3. Results and discussion

We initiated our studies with the addition of 1 equiv. of pinB-SePh (**4**) to the electron deficient alkyne 4-phenyl-3-butyn-2-one (**31**), in THF at room temperature, but no product formation was observed after the aqueous work up (Table 3.2, entry 1). By increasing the temperature up to 50 ºC the β-(phenylseleno)-α,β-unsaturated ketone **32** was obtained in 48% conversion in a ratio **Z-32/E-32** = 78/22 (Table 3.2, entry 2). Both stereoisomers could be isolated and characterized by NMR spectroscopy studies, and were assigned contrarily to Santi's previously reported data.[16]
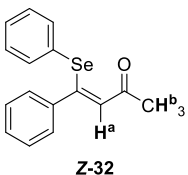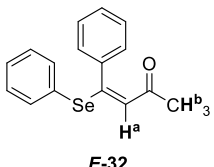
My co-worker Xavi Sanz computed the ^{1}H NMR shifts by DFT calculations and the results confirmed our assignment of stereoisomers. The computational results and the experimental results are summarized in Table 3.1 to be compared.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

The calculations predict that the proton in the *Z*-isomer must appear at higher chemical shift than in the **E-32** stereoisomer.

Table 3.1. Comparison of the computed ^{1}H NMR shift with the experimental values.

		δ (**Ha**)	δ (**Hb**)
	Santi's Work[16]	5.94 ppm	1.74 ppm
Z-32	Our experimental work	6.49 ppm	2.35 ppm
	Computed simulation	7.48 ppm	2.28 ppm
	Santi's Work[16]	6.83 ppm	2.37 ppm
E-32	Our experimental work	5.91 ppm	1.72 ppm
	Computed simulation	7.09 ppm	1.46 ppm

The computed vinylic protons appear slightly overshifted respect our experimental work but the differences are similar for both cases. In the case of the methyl protons the computed shifts are very well predicted and the values are very close to our experimental shifts

To find the optimal reaction conditions for the selenoboration of *α,β*-acetylenic ketones, we took the 4-phenyl-3-butyn-2-one (**31**) and run the reaction with different amounts of pinB-SePh (**4**). By increasing the amount of **4** up to 2 equivalents, we afford the desired product in 84% conversion (Table 3.2, entry 3) and with the same ratio of *Z*/*E* isomers as in the case of the reaction carried out with 1 equivalent (Table 3.2, entry 2). More equivalents of phenylseleno dioxaborolane (pinB-SePh (**4**)) afforded less conversion but the selectivity was slightly increased (Table 3.2, entry 4).

Keeping the 2 equivalents of pinB-SePh (**4**) as the optimized amount of reagent but increasing the temperature up to 70 ºC, the conversion did not improve (Table 3.2, entry 5). A possible explanation to this fact is due to the decomposition of the B-Se reagent before the interaction with the substrate.

62

Shorter reactions times did not change the *Z/E* ratio (Table 3.2, entries 6 and 7). Changing the solvent from THF to methanol afforded **Z-32** with high stereoselectivity and with full conversion (Table 3.2, entry 8).

Table 3.2. Optimization of the reaction conditions of pinB-SePh (**4**) with **31** [a]
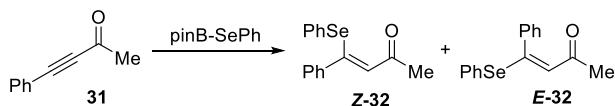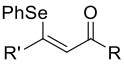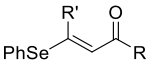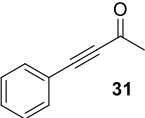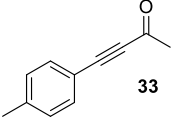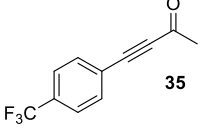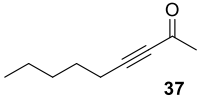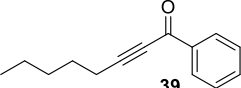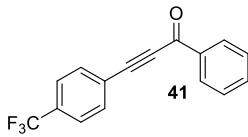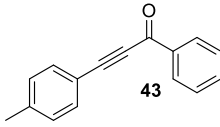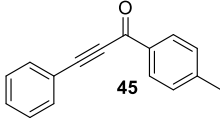

Entry	pinB-SePh (4)	Temp.	Time	Solvent	Conversion[b] (%)	Selectivity[b] 32-*Z*/32-*E*
1	1 equiv.	r.t.	16 h	THF	-	-
2	1 equiv.	50 °C	16 h	THF	48	78/22
3	2 equiv.	50 °C	16 h	THF	84	79/21
4	3 equiv.	50 °C	16 h	THF	30	83/17
5	2 equiv.	70 °C	16 h	THF	36	79/21
6	2 equiv.	50 °C	6 h	THF	54	82/18
7	2 equiv.	50 °C	3 h	THF	46	80/20
8	2 equiv.	50 °C	16 h	MeOH	99	99/1

[a] All reactions were carried out at 0.1 mmol scale of substrate. [b] Conversion and regioselectivity determined by NMR spectroscopy.

Under the optimized reaction conditions, 2 equivalents of pinB-SePh (**4**), 50 °C and MeOH as solvent, the selenoboration/protonolysis produced **Z-32** in 85% isolated yield (Table 3.3, entry 1).

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

Table 3.3. Selenoboration/protonolysis of α,β-acetylenic ketones [a]

Entry	Substrate	Conv. (%)[b]	PhSe–C=C(R')–C(O)–R	R'(PhSe)C=C–C(O)–R
1	31	99	99[87] (**Z-32**)	nd
2	33	99	95[86] (**Z-34**)	5 (**E-34**)
3	35	99	86[81] (**Z-36**)	14 (**E-36**)
4	37	99	95[88] (**Z-38**)	5 (**E-38**)
5	39	99	92[58] (**Z-40**)	8 (**E-40**)
6	41	99	99[84] (**Z-42**)	nd
7	43	99	90[84] (**Z-44**)	10 (**E-44**)
8[c]	45	99	99[85] (**Z-46**)	nd

[a] Reaction conditions: Substrate (0.1 mmol), pinB-SePh (2 equiv.), MeOH (2 mL), 50ºC, 16 h. [b] Conversion and regioselectivity determined by NMR spectroscopy. Values in parenthesis are isolated yields.

When we studied the generality of the reaction, we observed that methyl or aryl ketones did not affect the reaction outcome. In all cases the substrate was transformed into the desired vinyl selenides with high conversion and

selectivities. All the reactions performed showned high to quantitative *Z/E* ratio.

However, electron donating or electron withdrawing substituents in the phenyl group on substrates such as 4-(4-methylphenyl)-3-butyn-2-one (**33**) and 4-(4-trifluoromethylphenyl)-3-butyn-2-one (**35**), modified the stereoselectivity from ratio **Z-34**/**E-34** = 95/5 to **Z-36**/**E-36** = 86/14 (Table 3.3, entries 2 and 3). This outcome could be attributed to the fact that electron withdrawing substituents in the substrate modifies the energetic profile of the protonation step that is where the stereoselectivty seems to be determined.

Substrate **37**, 3-nonyn-2-one, containing an alkylic substituent in the *β*-position was also efficiently transformed into the *α*,*β*-seleniated product with a stereoisomeric ratio of **Z-38**/**E-38** = 95/5 (Table 3.3, entry 4). The phenyl substituent in the ketone group in substrate 1-phenyloct-2-yn-1-one (**39**) did not affect significantly the reactivity and similar results were obtained with **Z-40**/**E-40** = 92/8 stereoselectivity (Table 3.3, entry 5).

Full stereoselectivity was achieved for 1,3-diphenylprop-2-yn-1-one substrates **41** and **45** (Table 3.3, entries 6 and 8) with a slight decrease on stereoselectivity on the transformation from 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (**43**) to **44-Z**/**44-E** = 90/10 (Table 3.3, entry 7). These results suggest that the phenyl group in the ketone facilitates the slenoboration/protonolysis in all the cases, except for the electrondonating substituents on the aryl group of **43**.

To confirm the stereochemistry around the double bond, we crystallized the solid **Z-46** using acetonitrile/pentane system at room temperature. The full characterization of **Z-46**, allows us to confirm the *Z*-configuration of the vinyl chalcogenides (Figure 3.1).

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones
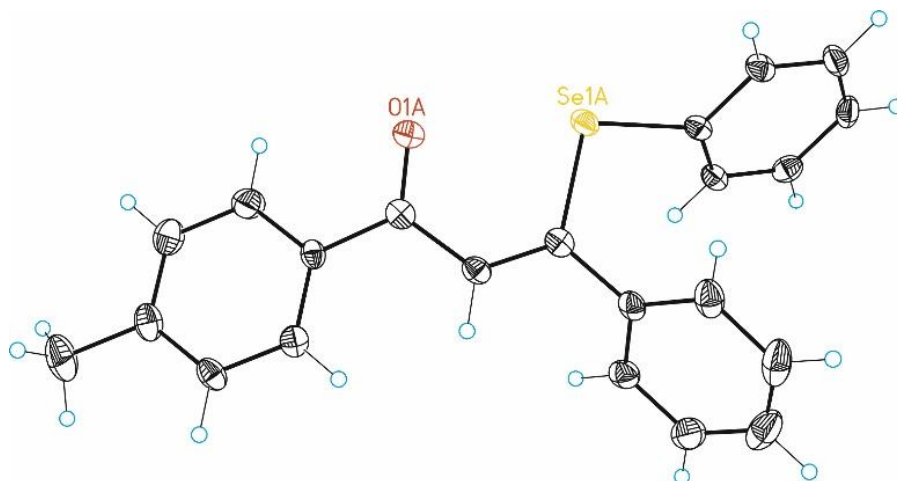
Figure 3.1. X-Ray Diffraction figure of **Z-46**.

This straightforward synthesis of (*Z*)-*β*-(arylseleno)-*α*,*β*-unsaturated ketones through selenoboration/protonolysis of ynones with pinB-SePh (**4**) simplified previous attempts *via* metal catalyzed methodologies, as well as the reaction conditions involved.
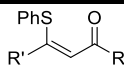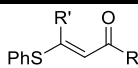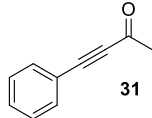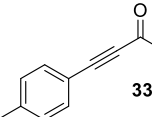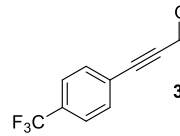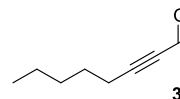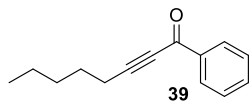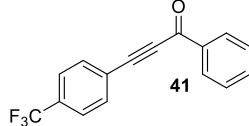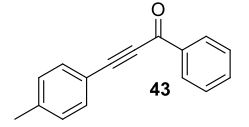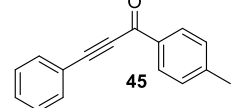
Our next goal was to extend the assembly protocol to thiodioxaborolanes pinB-SPh (**1**) and pinB-SBn (**3**) to synthesize vinyl sulfides from accessible ynones (Scheme 3.12).
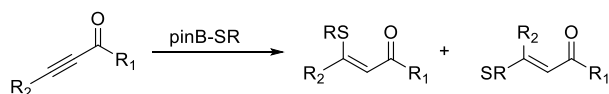
Scheme 3.12. Reactivity of thiodioxaborolanes to *α*,*β*-acetylenic ketones.

Under the same reaction condition used for selenoboration/protonolysis of *α*,*β*-acetylenic ketones, we started the study of the reactivity of **1** and **3** with ynones. The results obtained from the *1,4*-addition of pinB-SPh (**1**) group to *α*,*β*-acetylenic ketones are shown in Table 3.4.

Table 3.4. Thioboration/protonolysis of α,β-acetylenic ketones with pinB-SPh (**1**) [a]

Entry	Substrate	Conv. (%)[b]	PhS–C(R')=CH–C(O)–R	R'–C(SPh)=CH–C(O)–R
1	**31**	99	73[69][d] (**Z-47**)	27 (**E-47**)
2	**33**	99[80][c]	70 (**Z-48**)	30 (**E-48**)
3	**35**	99	76[65][d] (**Z-49**)	24 (**E-49**)
4	**37**	99	64[57][d] (**Z-50**)	36[30][e] (**E-50**)
5	**39**	99[68][c]	47 (**Z-51**)	53 (**E-51**)
6	**41**	99[85][c]	78 (**Z-52**)	22 (**E-52**)
7	**43**	99	76[59][d] (**Z-53**)	24 (**E-53**)
8[c]	**45**	99	76[69][d] (**Z-54**)	24 (**E-54**)

[a] Reaction conditions: α,β-acetylenic ketones (0.1 mmol), pinB-SPh (2 equiv.), MeOH (2 mL), 50 ºC, 16 h. [b] Conversion and regioselectivity determined by NMR spectroscopy. [c] Values in parenthesis are isolated yields of both stereoisomers. [d] Values in parenthesis are isolated yields of the Z-stereoisomer. [e] Values in parenthesis are isolated yields of the E-stereoisomer.

It can be highlighted that all examples gave full conversions with regioselectivity toward the C_β position and this reaction presents a stereoselectivity ratio around $Z/E \approx 3/1$.

Chapter 3

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

For substrate **31**, 4-phenylbut-3-yn-2-one, that has a phenyl substituent at the *beta* position, the thioboration/protonolysis provided complete conversion with 73% of stereoselection towards **Z-47** and 27% to product **E-47** (Table 3.4, entry 1). The presence of a methyl group or a trifluoromethyl group in the *para*-position, 4-(4-(trifluoromethyl)phenyl)but-3-yn-2-one (**35**) and 4-(*p*-tolyl)but-3-yn-2-one (**33**) respectively, did not modify neither the conversion not the stereoselectivity (Table 3.4, entries 2 and 3).
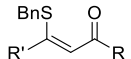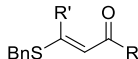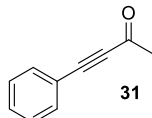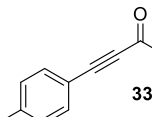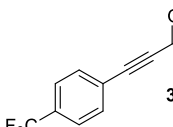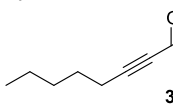
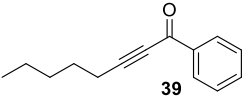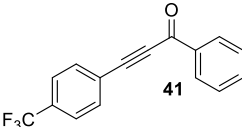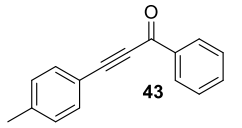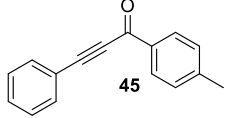The change of the phenyl group for an alkylic chain influenced the stereoselection and product **50** was observed with a ratio: **Z-50**/**E-50** = 64/36 (Table 3.4, entry 3). This result was also observed for 1-phenyloct-2-yn-1-one (**39**). In this case, the relative formation of the *E* isomer was favoured giving a stereoselectivity ratio of **Z-51**/**E-51** = 47/53 (Table 3.4, entry 4).

For substrates 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**41**), 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (**43**) and 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**45**), that presents aryl substituents in both sides of the triple bond and ketones, but with different electronic properties, the desired products were obtained with quantitative conversions and with a similar stereoselectivity among them (Table 3.4, entries 6-8).

After studying the reaction scope for the β-phenylthiolation/protonolysis of ynones our next goal was to observe the effect of changing the substituent in the sulfur atom from a phenyl substituent to a benzyl one. For that reason, we carried out the β-BnS addition to ynones using pinB-SBn (**3**) as reagent.

The results obtained for the reaction of α,β-acetylenic ketones with benzylthiodioxaborolane are summarized in Table 3.5 In all cases the products are obtained in quantitative conversions and with a prefered stereoselection towards the *Z*-isomer.

Table 3.5. Thioboration/protonolysis of α,β-acetylenic ketones with pinB-SBn (**3**)[a]

Entry	Substrate	Conv. (%)[b]	BnS, R' / O / R'—R (Z)	R', O / BnS—R (E)
1	**31**	99	71[65][d] (**Z-55**)	29 (**E-55**)
2	**33**	94[83][c]	72 (**Z-56**)	28 (**E-56**)
3	**35**	99	74[62][d] (**Z-57**)	26 (**E-57**)
4	**37**	99	58[52][d] (**Z-58**)	42[38][e] (**E-58**)
5	**39**	99[75][c]	59 (**Z-59**)	41 (**E-59**)
6	**41**	99[83][c]	75 (**Z-60**)	25 (**E-60**)
7	**43**	99	72[64][d] (**Z-61**)	28 (**E-61**)
8[c]	**45**	98	85[65][d] (**Z-62**)	15 (**E-62**)

[a] Reaction conditions: α,β-acetylenic ketones (0.1 mmol), pinB-SBn (2 equiv.), MeOH (2 mL), 50 °C, 16 h. [b] Conversion and regioselectivity determined by NMR spectroscopy. [c] Values in parenthesis are isolated yields of both stereoisomers. [d] Values in parenthesis are isolated yields of the *Z*-stereoisomer. [e] Values in parenthesis are isolated yields of the *E*-stereoisomer.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

The presence of aryl groups in the C_β, independently of the electronic properties of the substituents in the *para*-position and if the ketone has a methyl or a phenyl group in the *alpha* position (substrates **31**, **33**, **35**, **41** and **43**), afforded the desired products (**55-57** and **60-61**) in a similar stereoselective ratio about $Z/E = 7/3$ (Table 3.5, entries 1-3 and 6-7).

The stereoselectivity was affected when the substituent in the *beta* position is not able to extend the conjugation of the substrate as in of **37** and **39** that presents an alkylic chain in the *beta* position. With these substrates, the stereoselectivity was decreased to ***Z*-58**/***E*-58** = 58/42 and ***Z*-59**/***E*-59** = 59/41 (Table 3.5, entries 4 and 5).

In the 1,4-addition reaction of pinB-SBn (**3**) to ynones the stereoselection was slightly improved in 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**45**) that has a tolyl substituent in the ketone. The ***Z*-62** and ***E*-62** isomers were obtained in 85% and 15% respectively.

Comparing the results obtained in Table 3.4 and the ones shown in Table 3.5 can be said that the synthesis of vinyl sulfides through the reaction of thiodioxaborolane reagents and α,β-acetylenic ketones is not affected significantly by the substituents in the substrate, neither by the sulfur substituent in pinB-SR. Except on substrates **37** and **39**, that have an alkylic chain in C_β, which present a relative lower stereoselectivity.

The face to face reactivity of thiodioxaborolanes and ynones afforded in most of the cases the (*Z*)-β-thiolated-α,β-unsaturated ketone. This fact is in contrast with the lower stereoselectivity observed in alternative methodologies such as the addition of thiols to the electrondeficient alkynes, methyl propiolate and dimethyl acetylenedicarboxylate, in the presence of Ru catalysts.[17]

Based on the previous knowledge on the mechanism for the 1,4-addition of pinB-SR and pinB-SePh to α,β-unsaturated ketones and aldehydes, we suggested that the formation of vinyl selenides and sulfides follows a similar pathway.

Our mechanistic proposal started by considering the interaction of the carbonylic oxygen with the empty p orbital of the boron atom in the pinB-YR molecule to activate the B-Y bond. This interaction increases the nucleophilicity of the sulfur moiety because the lone pair of the sulfur cannot be partially delocalized in the boron empty orbitals. This gain of nucleophilicity allows the attack to the C_β of the substrate by the RY moiety forming an allene intermediate that finally undergoes protonolysis to yield the corresponding products (Scheme 3.13).
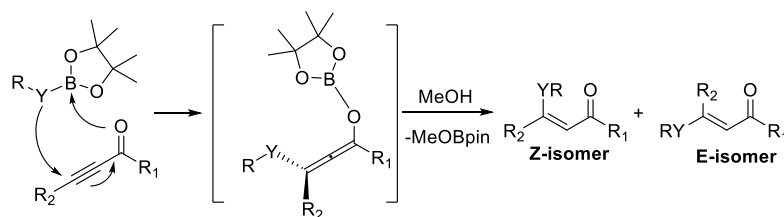
Scheme 3.13. Mechanistic proposal for the addition to ynones.

This mechanistic proposal was confirmed by means of DFT calculations carried out by my co-worker Xavi Sanz. The Gibbs free energy profile for the reaction of the model yonone 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**45**) with pinB-SePh (**4**) appears in Scheme 3.14. The activation of **4** 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 one leading to the 1,2-addition product and the pathway towards the 1,4-addition products.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones
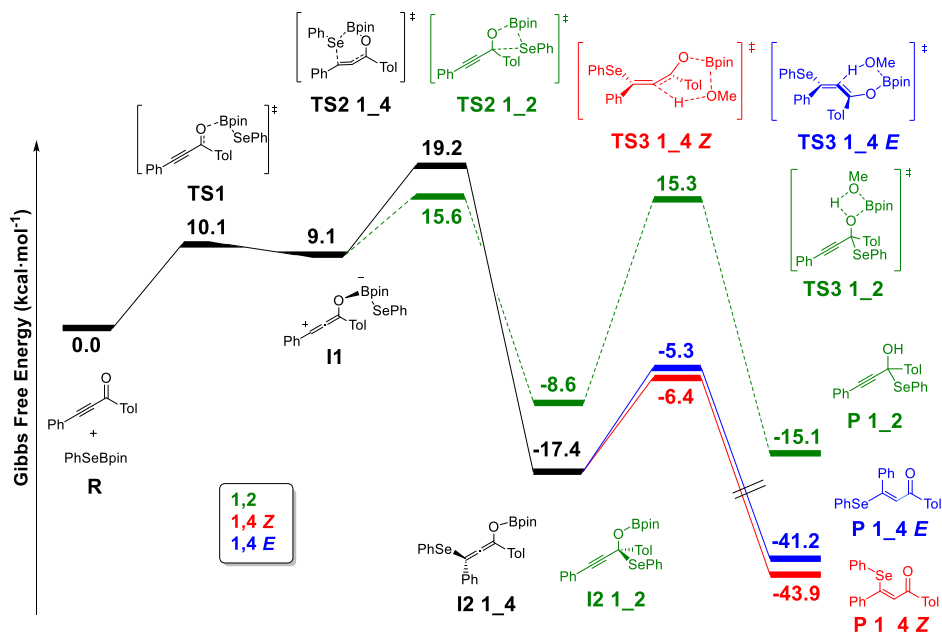
Scheme 3.14. Relative Gibbs free energies for the reaction of **4** with **45**. All energies are in kcal·mol^{-1}. This calculation was carried out by Xavi Sanz under the supervision of Dr. Bo.

The attack of the nucleophilic PhSe moiety to the carbonyl group through the **TS 1_2** is one possible reaction pathway and leads to the formation intermediate **I2 1_2**. This intermediate can finally undergo protonolysis with methanol through the **TS3 1_2** to form the 1,2-addition product **P 1_2** and the byproduct pinB-SPh (Scheme 3.14, green pathway). Considering the pathway for the Michael addition, after the **TS2 1_4** occurs, an allene intermediate is formed (**I2 1_4**). This intermediate con 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 **Z-46** and **E-46** respectively.

In the reaction crudes, there is no evidence for the formation of the 1,2-addition product. This observation is in agreement with the DFT calculations.

72

The reaction pathway for the 1,2-addition is disfavored due to the low stability of the **I2 1_2** and the high-energy barrier for the **TS3 1_2** of the protonolysis.

Moreover the 1,4-addition pathway takes place through a more stable intermediate **I2 1_4** and the protonation step has a low energy barrier compared with the 1,2-addition pathway. In addition, the products formed (**P 1_4 Z** and **P 1_4 E**) are more stable due to their low energy values.

Experimentally **46-Z** was exclusively obtained and this is in good agreement with the DFT calculations. Comparing the **TS3 1_4 Z** and **TS3 1_4 E** it can be observed that the intermediate leading the *Z*-product is 1.1 kcal·mol^{-1} less energetically demanding that the intermediate giving the *E*-product. Also, the **P 1_4 Z** is 2.7 kcal·mol^{-1} more stable that the product with the opposite conformation. These two facts show that the product with the *Z*-geometry at the double bond is favored kinetically and thermodynamically.

When the reaction pathway for the substrate **45** with reagent pinB-SPh (**1**) was calculated, the same conclusions were obtained. The *Z*-isomer (**Z-54**) was more stable than the *E*-isomer due to a less energetically demanding transition state.

When the energy profile for the reaction of 1-phenyl-2-octyn-1-one (**39**) with pinB-SPh (**1**) was calculated, a different outcome was observed. The propargylic alkyl chain in the substrate seems to favor the *E* isomer thermodynamically although the *Z* isomer should be kinetically favored. As both activation energies for the **TS3 1_4** are not very high, they can be both easily achieved.
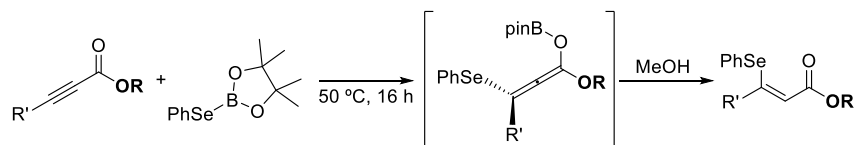
3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

Once the 1,4-adition of pinB-SePh (**4**), pinB-SPh (**1**) and pinB-SBn (**3**) to ynones has been covered, from experimental ant theoretical point of view, we wanted to extend this methodology to electron-deficient α,β-acetylenic esters.

Before starting the experimentation, some DFT calculations were run by the co-worker Diego Garcia to study the differences in the energy profiles between the reactions of phenylselenodioxaborolanes with ynones or ynoates. Despite the fact that the calculated energy barrier for the 1,4-addition of pinB-SePh (**4**) is higher for the α,β-acetylenic esters (31.9 kcal/mol) than for the α,β-acetylenic ketones (19.2 kcal/mol), experimentally we observed that at 50 °C the reaction of pinB-SePh (**4**) with α,β-acetylenic esters can also take place affording the β-selenated products.

Experimentally we explored the reactivity with representative substrates that combines aryl and alkyl groups in the β-position, as well as sterically differentiated esters groups. The starting reaction conditions were the same as for the selenoboration/protonolysis of acetylenic ketones, and after optimization it was found that substrate **63**, could be quantitatively performed with 1.1 equivalents of pinB-SePh (**4**). In Table 3.6 is summarized the results for the substrate scope of the β-selenation/protonolysis of α,β-acetylenic esters.

74

Table 3.6. *β*-Selenation of *α,β*-acetylenic esters, *via* 1,4-selenoboration/ protonolysis [a]

Entry	Substrate	Product	NMR yield (%)[b]	I.Y. (%)[c]
1	**63**	**Z-64**	82	74
2	**65**	**Z-66**	90	79
3	**67**	**Z-68**	89	78
4	**69**	**Z-70**	75	72
5	**71**	**Z-72**	88	69

[a]Reaction conditions: *α,β*-acethylenic esters (0.2 mmol), pinB-SePh (1.1 equiv.), MeOH (0.15 mL), at 50 ºC for 16 h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c]I.Y.= isolated yield.

The substrate ethyl 3-phenylpropiolate (**63**) afforded the product ethyl (*Z*)-3-phenyl-3-(phenylselanyl)acrylate (**Z-64**) in a moderate NMR yield with high regioselectivity towards the *beta* position and stereoselectivity towards the *Z*-isomer (Table 3.6, entry 1). When the reaction was performed with **65**, a slightly improvement of the conversion was detected in the formation of the product **Z-66** presenting a *Z*-conformation in the double bond (Table 3.6, entry 2). This improvement could be due to the MeO nature of the ester group.

Chapter 3

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

The formation of the *β*-selenated-*α,β*-unsaturated ester was not significantly affected by adding an electron donating group in the *beta* position as in the case of ethyl 3-(4-methoxyphenyl)propiolate (**67**) (Table 3.6, entry 3). To study the effect of the ester substituent, we run the reactions with substrate **67**, propyl 3-(4-methoxyphenyl)propiolate (**69**) and isopropyl 3-(4-methoxyphenyl)propiolate (**71**) which contain the EtO⁻, PrO⁻ and *i*PrO⁻ group respectively (Table 3.6, entries 3-5). No significant effect on the conversion was observed. It seems that it is a robust methodology because neither steric nor electronic changes introduced in the substrates affected the 1,4-selenoboration followed by protonolysis towards the desired *β*-selenated *α,β*-unsaturated esters.

The exclusive formation of the *Z*-isomer was confirmed by spectroscopic on the full characterization of product **Z-64** by X-Ray diffraction (Figure 3.2). The single crystal was obtained from a mixture of acetonitrile and pentane at room temperature.
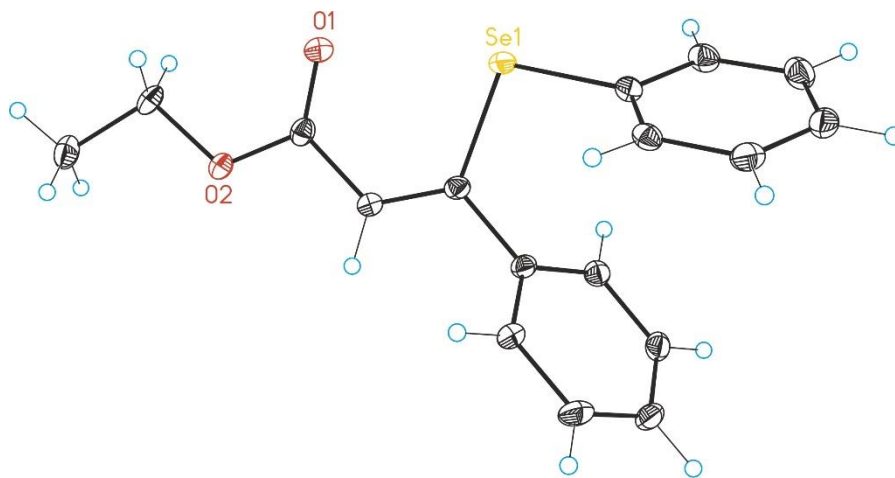
Figure 3.2. X-Ray Diffraction figure of **Z-64**.

The proposed mechanism for this reaction follows the same pathway as in the case of ynones. The activation of boron atom through the interaction of the lone pair of the oxygen of the carbonyl with its *p*-empty orbital group leads to intermediate **A**.

In this intermediate the nucleophilicity of the PhSe- moiety is enhanced, this fact allows the selenium attack to the electrophilic position of the *β* carbon of the triple bond yielding the 1,4 selenoborated allene intermediate **B**. After protonolysis of the intermediate **B** with methanol, the desired *β*-phenylselenium-*α*,*β*-unsaturated ester is formed with a preferred *Z*-conformation (Scheme 3.15).
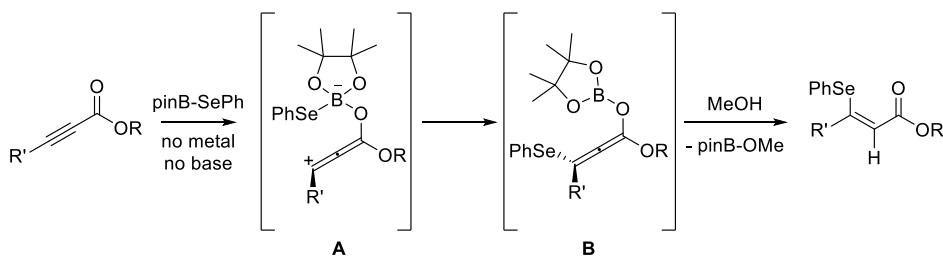
Scheme 3.15. Mechanistic proposal for the addition to *α,β-acetylenic esters*.

In 2012, our group reported the role of trialkyl phosphines in the *β*-boration reaction of *α,β*-unsaturated carbonyl compounds without using any Brönsted bases. The PR$_3$ becomes essential to interact with the substrate resulting in the formation of a phosphonium cation that forms an ion pair with a borate anion (Scheme 3.16).[18]
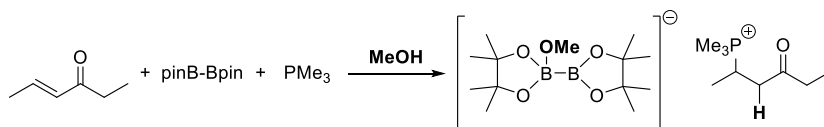
Scheme 3.16. Ion pair formation by methoxy borate complex and phosphonium.

When a phosphine interacts with an *α,β*-acetylenic ester, the formation of a zwitterionic phosphonium allenolate is expected (Scheme 3.17).[19]

This kind of zwitterionic species change the reactivity pattern of the triple bond, redirecting the nucleophilic attack from the normal β-position to the abnormal α-position.[20]
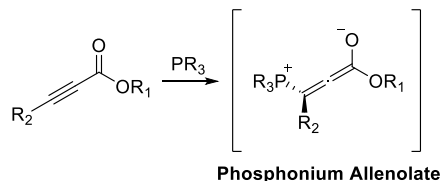

Scheme 3.17. Formation of a zwitterionic phosphonium allenolate

In 1997, Trost and co-workers studied the phosphonium intermediate formation for the synthesis of dehydroamino acids derivatives. They were able to add phthalimide or sulfonamides in the *alpha* position of ethyl phenylpropiolate. The desired products were obtained in moderate to high yields and with high regioselectivity to the C_α (Scheme 3.18).[21]
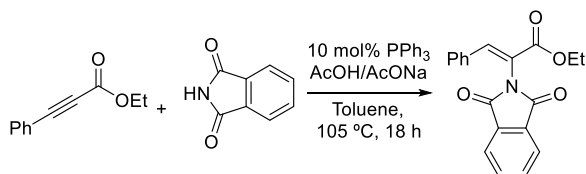
Scheme 3.18. α-Addition of nitrogen nucleophiles to conjugated alkynoates

Later, in 2002, it was reported a tandem reaction to construct heterocycles. The first reaction was a phosphine-catalyzed umpolung addition and then an intramolecular conjugate addition. When ethyl propiolate was mixed with a bifunctional nucleophile in the presence of catalytic amount of triphenylphosphine, the tandem reaction took place leading the desired heterocycle (Scheme 3.19).[22]
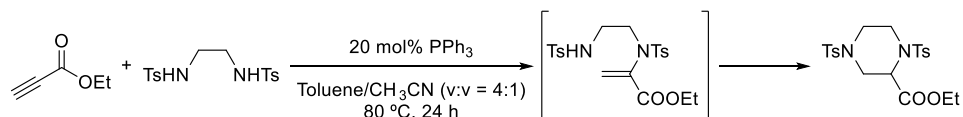
Scheme 3.19. Synthesis of heterocycles *via* phosphine-catalyzed umpolung addition and intramolecular conjugate addition.

78

More recently, Sawamura and co-workers took advantage of the phosphine addition to ynoates to perform the *3,4-anti*-addition of silylboranes and diboranes.

They used tributylphosphine as catalyst and performed the reaction without solvent at 80 ºC, for 8 hours. The *3,4-anti*-silaborated products are obtained in moderated to high yields (Scheme 3.20), with the C-Si bond located in the *alpha* position.
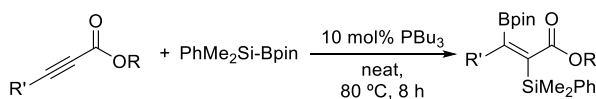
Scheme 3.20. Phosphine-catalyzed silaboration of α,β-acetylenic esters.

The postulated reaction mechanism (Scheme 3.21) starts with the interaction of the phosphine with the substrate forming the zwitterionic allenolate intermediate **A** which is further stabilized by the interaction of the negative charge of the oxygen with the empty p orbital of the silylborane. This later interaction increase the nucleophilicity of the silicon atom that attacks the sp carbon of the allene, which is the most electrophilic position. This attack generates the ylide intermediates (**B1/B2**). Next, the ylide carbon of **B2** attacks the B-atom to form borate **C**. Finally, the B-O bond is cleavage producing the elimination of PBu$_3$ and affording the *3,4-anti*-silaborated product.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones
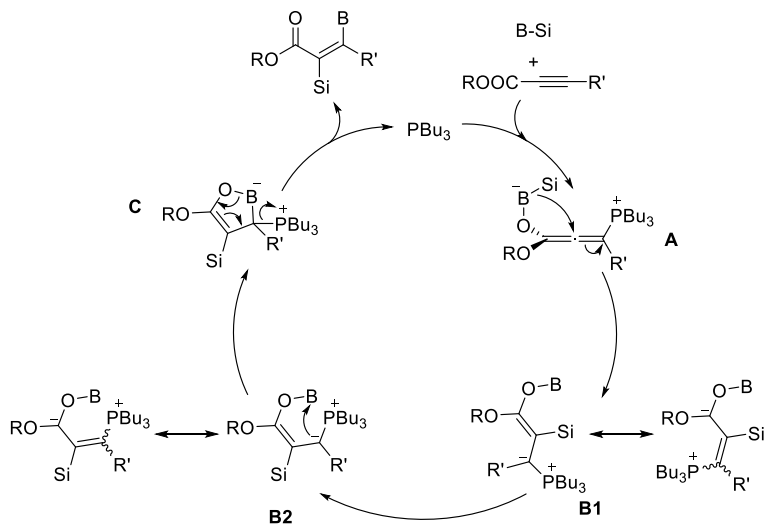
Scheme 3.21. Mechanism for the silaboration of ynoates proposed by Sawamura

With all this precedents in mind, we wanted to perform the *3,4-anti*-selenoboration of *α,β*-acetylenic esters with pinB-SePh (**4**) catalyzed by a phosphine.

Using ethyl phenylpropiolate (**63**) as a model substrate, we run the first reaction with pinB-SePh (**4**) under the Sawamura's reaction conditions. When the substrate and the phosphine were together in the schlenck tube a change of color from yellow to red was observed. This fact might be due to the interaction of the phosphine to the *beta* position. However, no desired product was observed (Table 3.7, entry 1).

Then we performed the reaction under the same conditions but with less basic phosphines, shuch as PCy$_3$ and PPh$_3$. In the case of PCy$_3$ the desired product was detected in a 66% NMR yield (Table 3.7, entries 2-3). In the absence of phosphine, the reaction did not take place. (Table 3.7, entry 4). Shorter reaction times seems not to affect to the product formation (Table 3.7, entry 5). Since **4** suffers from thermal decomposition, running the reaction at room temperature was the next attempt but conversion to the

3,4-anti-selenoborated product was similar to the one at 50 °C (Table 3.7, entry 6).

When the amount of phosphine was increased to 15 mol% the product formation was improved up to 71% NMR yield (Table 3.7, entry 7). In order to get a better stirring of the reaction, 0.15 mL of THF was added. Increasing the amount of pinB-SePh did not improve the reaction outcome (Table 3.7, entries 8 and 9).

**Table 3.7.** Optimization for the *3,4-anti*-selenoboration of **61** with pinB-SePh (**4**) [a]
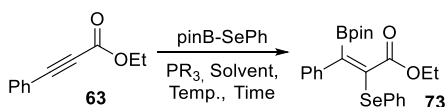
Entry	PR$_3$	pinB-SePh	T (°C)	Time (h)	NMR Yield[b] (%)
1	10 mol% PBu$_3$	1.1 equiv.	50 °C	16 h	-
2	10 mol% PPh$_3$	1.1 equiv.	50 °C	16 h	-
3	10 mol% PCy$_3$	1.1 equiv.	50 °C	16 h	66%
4	-	1.1 equiv.	50 °C	16 h	-
5	10 mol% PCy$_3$	1.1 equiv.	50 °C	8 h	66%
6	10 mol% PCy$_3$	1.1 equiv.	r.t.	8 h	67%
7[c]	15 mol% PCy$_3$	1.1 equiv.	r.t.	8 h	71%
8[c]	15 mol% PCy$_3$	1.5 equiv.	r.t.	8 h	65%
9[c]	15 mol% PCy$_3$	2 equiv.	r.t.	8 h	67%

[a] All reactions are carried out at 0.2 mmol scale of substrate. [b] NMR Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c] The reaction was run with 0.15 mL of THF to solubilize all the solids.

The optimized conditions for ethyl phenylpropiolate (**63**) were 15 mol% of PCy$_3$, with 1.1 equiv. of **4**, in THF (0.15 mL) at room temperature for 8 hours but when the scope was extended, it was found that 16 hours of reaction was better for the generality of the reaction. The generality of the reaction was explored with substrates **67**, **69** and **71**.

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

The addition of the Bpin moiety at the β-position of the substrates is confirmed by NMR data and in particular by the interaction between the O from the carbonyl group and the B, with a shifted ^{11}B NMR signal to higher field (δ: 27-28 ppm), as it can be seen in products **74**, **76** and **78** (Scheme 3.22).
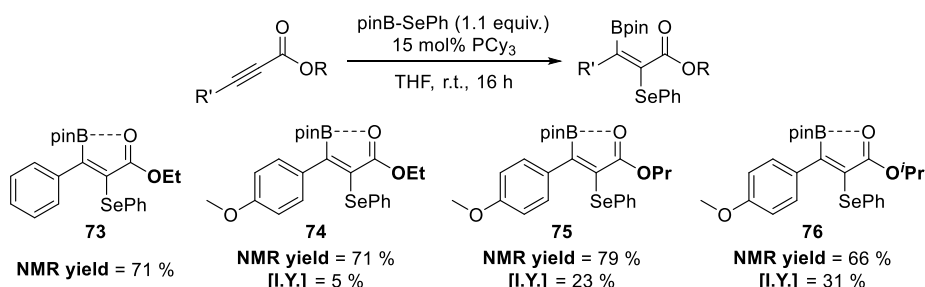
Scheme 3.22 *anti-3,4*-selenoboration of α,β-acetylenic esters.

When the reaction was performed with methyl non-2-ynoate **65** traces of the desired product were detected by NMR. This decrease on the product formation can be justify by possible phosphine induced isomerization of alkynoates to 2,4-dienoates (Scheme 3.23).[23]
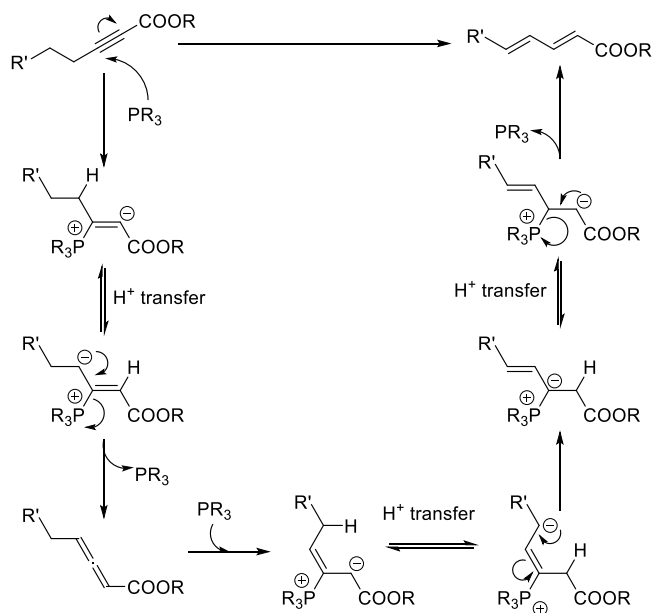
Scheme 3.23. Suggested mechanism for the phosphine induced isomerization of alkynoates to 2,4-dienoates.

Moderate NMR yields were obtained for the *3,4-anti*-selenoboration without being affected by the substituents next to the triple bond or the ester substituent, but low isolated yields were achieved after purification.

Deactivation of the silica with triethyl amine, to avoid decomposition of the *3,4-anti*-selenoborated products, results in a total retention in the column due to the adduct formation between the boron and the free amine.

To try to avoid this problem we decided to further functionalize the boron moiety due to its high versatility. We plan a one pot procedure to generate the corresponding *α*-phenylselenated compounds from the *anti*-3,4-selenoboration products *via* protodeboronation process. This methodology requires the treatment of the reaction crude with with K_2CO_3 at 70ºC for 2 h.[24] This one pot procedure afforded products **77**, **78**, **79** and **80** in moderate values, representing the first attempt to obtain those high valued products (Scheme 3.24).
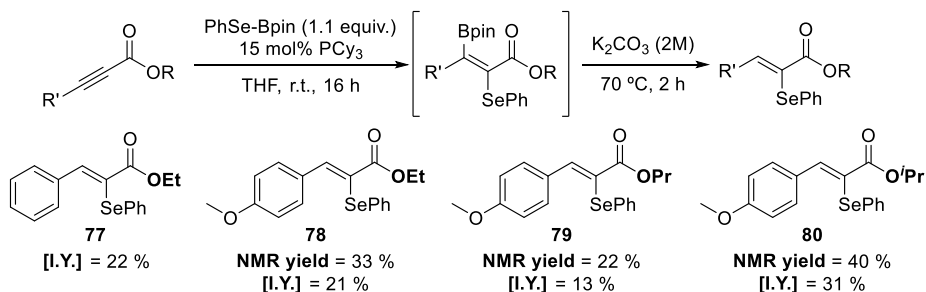
Scheme 3.24. *α*-Selenation of *α,β*-acethylenic esters *via anti-3,4*-selenoboration

3.4. Conclusions

We reported a more flexible and reliable route to stereodefined *Z*-alkenyl selenides and *Z*-alkenyl sulfides through the powerful "*pull-push*" properties of Bpin units in the chalcogenoborate reagents pinB-SePh (**4**), pinB-SPh (**1**) and pinB-SBn (**3**) when react with ynones. The reaction is performed in a metal free context without any additive except MeOH as solvent. The mechanistic proposal allows to justify and to understand the selectivity of the reaction outcome.

When the reaction is carried out in the presence of tricyclohexyl phosphine a different outcome is observed. The formation of an *anti*-3,4-selenoborated product takes place through the formation of a zwitterionic phosphonium allenolate. After protodeboronation process with K_2CO_3 at 70 ºC, the corresponding α-phenylselenated compounds were obtained in moderate values being the first reported method to synthesize these high valued compounds.

3.5. References

1 a) G. Perin, E. J. Lenardão, R. G. Jacob, R. B. Panatieri, *Chem. Rev.* **2009**, *109*, 1277–1301; b) T. Kondo, T.-a. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220; c) J. V. Comasseto, L. W. Ling, N. Petragnani, H. A. Stefani, *Synthesis* **1997**; *1997,* 373-403; d) T. Wirth, *Organoselenium Chemistry - Modern Developments in Organic Synthesis*, Topics in Current Chemistry Springer-Verlag: Heidelberg, **2000**; e) T. G. Back, *Organoselenium Chemistry: A Practical Approach*, Oxford University Press: New York, **1986**; f) C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press: Oxford, **1986**.

2 a) K. Itami, S. Higashi, M. Mineno, J.-i. Yoshida, *Org. Lett.* **2005**, *7*, 1219–1222; b) M. Tingoli, M. Tiecco, L. Testaferri, A. Temperini, G. Pelizzi, A. Bacchi, *Tetrahedron* **1995**, *51*, 4691-4700.

3 a) H. Zhang, B. Wang, H. Yi, Y. Zhang, J. Wang, *Org. Lett.* **2015**, *17*, 3322–3325; b) A. Armstrong, D. P. G. Emmerson, H. J. Milner, R. J. Sheppard, *J. Org. Chem.* **2014**, *79*, 3895–3907.

4 a) Q. Li, T. Dong, X. Liu, X Lei, *J. Am. Chem. Soc.* **2013**, *135*, 4996–4999; b) N. T. Tam, C.-G. Cho, *Org. Lett.* **2007**, *9*, 3391–3392; c) H. J. Reich, W. W. Willis, P. D. Clark, *J. Org. Chem.* **1981**, *46*, 2775–2784.

5 S. Braverman, M. Cherkinskya, Y. Kalendara, R. Janaa, M. Sprechera, I. Goldbergb, *Synthesis* **2014**, *46,* 119-125.

6 I. P. Beletskaya, V. P. Ananikov, *Eur. J. Org. Chem*. **2007**, *2007*, 3431–3444.

7 a) T. Kataoka, M. Yoshimatsu, H. Shimizu, M. Hori, *Tetrahedron Lett.* **1990**, *31*, 5927-5930. b) T. Kataoka, M. Yoshimatsu, Y. Noda, T. Sato, H. Shimizu, M. Hori, *J. Chem. Soc., Perkin Trans. 1* **1993**, 121-129.

8 C. Kashima, T. Tajima, M. Shimizu, Y. Omote, *J. Heterocycl. Chem.* **1982**, *19*, 1325-1328.

9 T. Sugita, M. Eida, H. Ito, N. Komatsu, K. Abe, M. Suama, *J. Org. Chem.* **1987**, *52*, 3789–3793.

10 C. -Q. Zhao, X. Huang, J. -B. Meng, *Tetrahedron Lett.* **1998**, *39*, 1933-1936.

11 D. J. Knapton, T. Y. Meyer, *J. Org. Chem.* **2005**, *70*, 785-796.

Chapter 3

3. 1,4-Addition of pinB-SR and pinB-SeR to ynones

12   F. Yamashita, H. Kuniyasu, J. Terao, N. Kambe, *Org. Lett.* **2008**, *10*, 101–104.

13   a) E. J. Lenardão, M. S. Silva, S. R. Mendes, F. de Azambuja, R. G. Jacob, P. C. S. dos Santos, G. Perin, *J. Braz. Chem. Soc.* **2007**, *18*, 943-950; b) G. Perin, S. R. Mendes, M. S. Silva, E. J. Lenardão, R. G. Jacob, P. C. dos Santos, *Synth. Commun.* **2006**, *36*, 2587-2595.

14   C. C. Silveira, R. B. Guerra, J. V. Comasseto, *Tetrahedron Lett.* **2007**, *48*, 5121–5124.

15   V. P. Reddy, K. Swapna, A. V. Kumar, K. R. Rao, *Synlett* **2009**, *17,* 2783-2788.

16   B. Battistelli, T. Lorenzo, M. Tiecco, C. Santi, *Eur. J. Org. Chem.* **2011**, *2011*, 1848–1851.

17   U. Koelle, C. Rietmann, J. Tjoe, T. Wagner, U. Englert, *Organometallics* **1995**, *14,* 703–713.

18   C. Pubill-Ulldemolins, A. Bonet, H. Gulyás, C. Bo, E. Fernández, *Org. Biomol. Chem.* **2012**, *10*, 9677-9682.

19   a) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035 –1050.

20   D. Tejedor, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, *Chem. Eur. J.* **2003**, *9*, 3122-3131.

21   B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596.

22   C. Lu, X. Lu, *Org. Lett.* **2002**, *4*, 4677–4679.

23   a) B. M. Trost, U. Kazmaier, *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935; b) C. Guo, X. Lu, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921-1923; c) S. D. Rychnovsky, J. Kim*, J. Org. Chem.* **1994**, *59*, 2659–2660.

24   W. T. Delgado, F. Shahin, M. J. Ferguson, R. McDonald, G. He, E. Rivard, *Organometallics* **2016**, *35*, 2140–2148.

"Happiness comes not from what we have

but from what we give and what we share."

Lady Olave Baden-Powell

Chapter 4

1,1-Addition of pinB-SR to trimethylsilyl

diazomethane followed by selective

alkylations

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

4.1. Introduction

Diazo compounds are ambiphilic reagents and constitutes a very versatile and powerful tool that have been extensively applied in synthetic organic chemistry.[1] The *gem*-difunctionalization to the carbon center of the diazo compound by the direct introduction of two functional groups, has attracted much attention recently.[2]

Among the reactivity of diazo compounds, it has been described three major reaction mechanisms for the dinitrogen elimination processes that involve different reactive intermediates.[3] The first methodology involves the formation of a metal-carbene species (Scheme 4.1, path *a*) from the corresponding diazo compound and a metal carbene. Another possibility is the one proceeding *via* a procarbonium ion intermediate (Scheme 4.1, path *b*), which occurs through the attack of the nucleophilic carbon center of the diazo group to an electrophile followed by the attack of an external nucleophile with the concomitant N_2 release. The third way involves the formation of the free carbene intermediate through thermolysis or photolysis (Scheme 4.1, path *c*).

a) Process via metal carbene
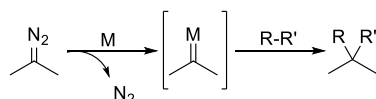
b) Process via procarbonium ion
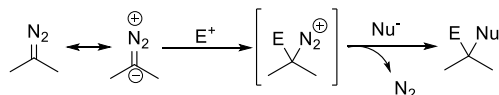
c) Process via free carbene
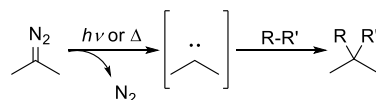
Scheme 4.1. Reaction mechanisms for the difunctionalization of diazo compounds.

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

Concerning the diazo compound reactivity *via* the metal-carbene, many reactions have been reported. For example, unsaturated double bonds can be converted into three-membered ring (epoxidation, cyclopropanation or aziridination).[4] Saturated bonds can also be functionalized *via* diazo compound insertion into the σ-bond.[5]

Rhodium and copper-based catalyst have been extensively used in the formation of the metal-carbene from the diazo compound to be inserted into the σ-bond.[6] For example the use of a rhodium(II)-catalyst afforded the alkoxylation/acetalization of substituted diazo compounds. The reaction proceeds at room temperature, in one hour, and yields the products wearing a substituted quaternary center in moderate yields (Scheme 4.2).[7]
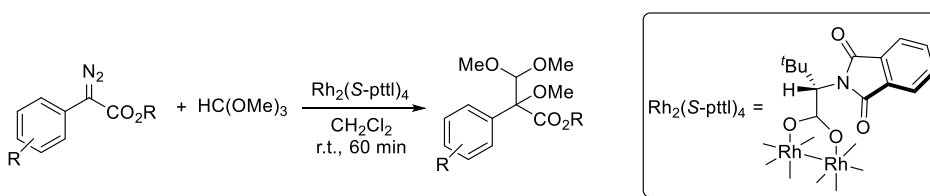
Scheme 4.2. Rhodium(II)-catalyzed diazo compound insertion into C-O bond.

In 2008, it was reported that a copper (II) can catalyze the carbenoid insertion into Si-H bonds. By using spirodiimine ligands, a wide range of α-silylesters were produced in high yields (Scheme 4.3).[8]
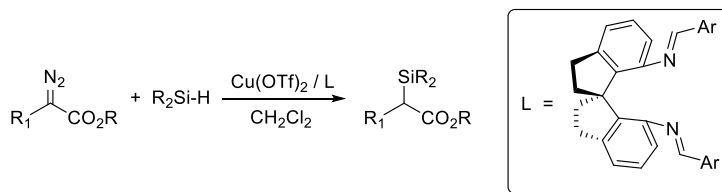
Scheme 4.3. Copper(II)-catalyzed diazo compound insertion into Si-H bond.

Concerning the metal-carbene formation from diazo compounds, gold(I) complexes has experimented a rapid development. In 2005 was reported the first of a gold-based catalyst for the decomposition of ethyl diazoacetate.[9]

90

By using a [(IPr)AuCl] catalyst they were able to generate the corresponding gold-carbene from ethyl diazoacetate and perform cyclopropanations, insertions into C-N and C-O bond (Scheme 4.4).
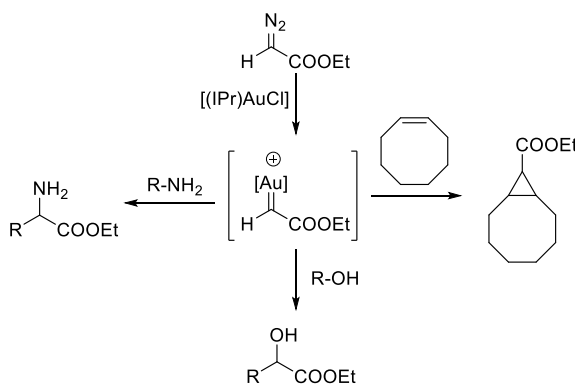
Scheme 4.4. Gold(I) catalyzed diazo compound insertion.

An example of reaction, that proceed *via* procarbonium ion intermediate, is the one reported by Murphy and co-workers. They were able to carried out the *α,α*-dihalogenation of diazoacetate derivatives. By using iodobenzene dichloride they were able to obtain the desired products in high yields and short reaction times (Scheme 4.5).[10] The pyridine is used in catalytic amount to activate the iodane to give electrophilic salt. When they used TolIF$_2$ they were able to perform the defluorination at the same position.
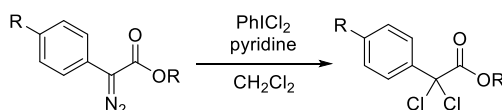
Scheme 4.5. Dichlorination reaction of diazoacetate derivatives.

Concerning processes *via* free carbene generated from thermolysis or photolysis from diazo compounds, Davies and co-workers reported in 2012 the thermal decomposition of aryldiazoacetates in the absence of a metal catalyst to be inserted into N-H bonds.[11]

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

The insertion of diazo compounds into boron containing reagents affords a valuable synthetic strategy towards the preparation of unprecedented organoboranes.[12]

The insertion of diazocompounds into B-H bonds has been described by the attack of the nucleophilic carbon center of the diazo group from diphenyl diazomethane to the B in catecholborane ($(C_6H_4O_2)BH$) to yield the corresponding organoborane in 97% yield within 2 h, at room temperature (Scheme 4.6).[13]
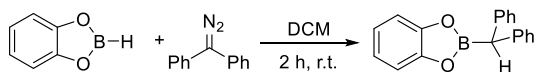
Scheme 4.6. Diphenyl diazomethane insertion into B-H bond of catecholborane.

Alternatively, certain Rh(I) complexes are able to catalyze the insertion of α-diazoketones into the B-H bonds of amine-borane adducts to give valuable α-boryl ketones. These Rh-catalyzed B-H insertions can be performed enantioselectively simply by using an appropriate chiral ligand.[14]
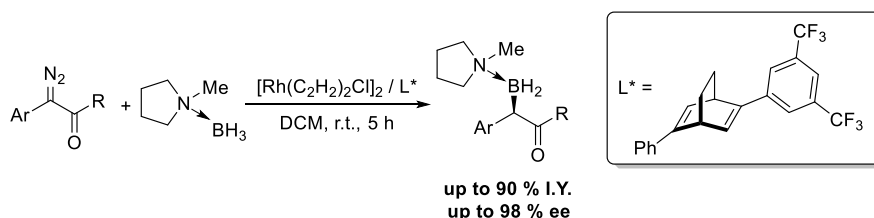
Scheme 4.7. Asymmetric B−H insertion reactions of α-diazoketones.

N-heterocyclic carbene-boranes (NHC-boranes), which are typically white solids, that are stable to air and water, react with diazocarbonyl compounds to promote the rhodium-catalyzed insertion into B-H bond. This reaction presents broad functional group tolerance in both the NHC-borane and diazo carbonyl component and produces α-NHC-boryl carbonyl compounds in moderate yields (Scheme 4.8).[15]
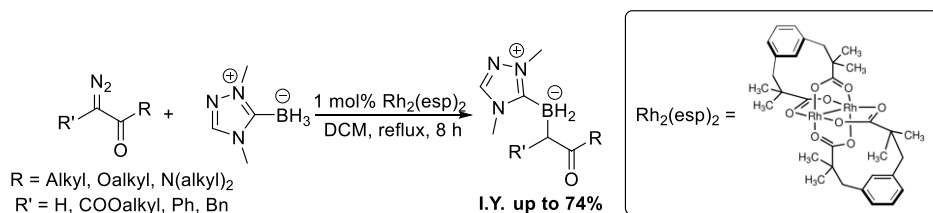
Scheme 4.8. Rh(II) catalyze insertion of diazo compounds into NHC-boranes.

At the same time it was reported the use of phosphine-borane adducts for diazocarbonyl compounds insertion. In this case, they used a copper (I) metal catalyst with a chiral spiro-bisoxazoline ligand to build a new C-B bond with high yield and enantioselectivity under mild reaction conditions (Scheme 4.9).[16]
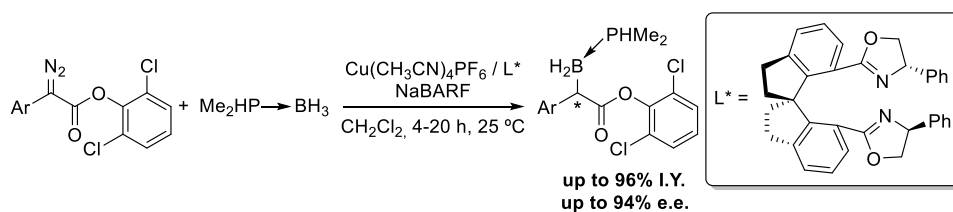
Scheme 4.9. Enantioselective copper-catalyzed B−H bond insertion reaction.

The insertion of diazo compounds into B-Cl bond is a good strategy to afford *α*-chloroboranes. B-chlorocatecholborane reacts rapidly with diazodiphenylmethane affording the inserted product at room temperature in 1 h. The final product was further stabilized by adding triethylphosphine oxide to generate the corresponding adduct (Scheme 4.10).[13]
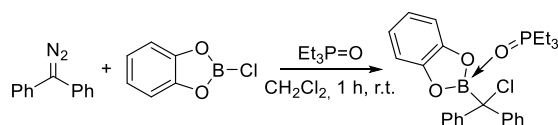
Scheme 4.10. Diazodiphenylmethane insertion into B-Cl bond.

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

1,1-diborylalkanes can be synthesized through insertion into B-B bond. Srebnik and co-workers reported that diazomethane can insert into B_2pin_2 using tetrakis(triphenylphosphine) platinum (0) as catalyst with high product formation (Scheme 4.11 a).[17] Later they optimized the reaction conditions to be able to use substituted diazo compounds to synthesize substituted α,α-diborilated products in moderate yields (Scheme 4.11, b).[18]
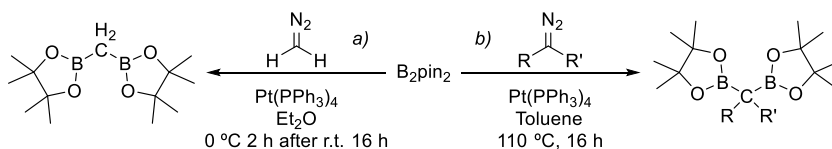
Scheme 4.11. Insertion of *a)* diazomethane and *b)* diazoalkanes into B_2pin_2.

The proposed mechanism for the insertion of substituted diazo compounds into bis(pinacolato)diboron reported by Srebnik and co-workers starts by an activation of the B-B bond by an oxidative addition of B_2pin_2 to the Pt(0) complex to form a bis-(boryl) platinum(II) intermediate (**A**). This is followed by the insertion of a generated carbene by thermal decomposition of the diazo compound into the B-Pt bond to form **B**, and finally a reductive elimination generates the desired product **C** (Scheme 4.12).
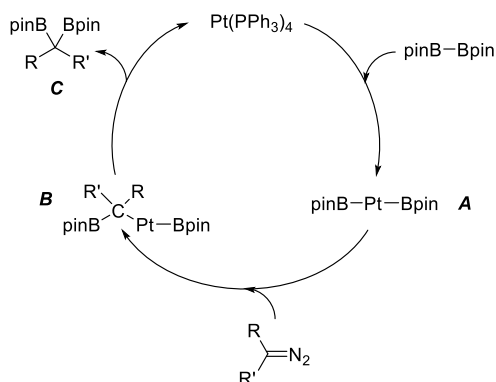
Scheme 4.12. Proposed catalytic cycle for the platinum catalyzed diazo compound insertion into bis(pinacolato)diboron.

94

In 2014, Kingsbury and co-workers extended the reaction scope of $Pt(PPh_3)_4$ catalyzed diazoalkanes insertion into B_2pin_2 and reported the concomitant C-B functionalization of the products through deboronation followed by substitution methodology.[19] This functionalization is complementary to the previous one reported by Shibata and co-workers where two consecutive Suzuki–Miyaura cross-coupling reactions were performed on 1,1-diborylalkanes.[20]

The insertion of diazo compounds into B-Si bond introduces simultaneously a silyl group at the same carbon as the boron moiety is introduced. The reaction of silyl-catecholborane with ethyl diazoacetate has been reported to generate the desired product in 3 hours at 0 ºC (Scheme 4.13).[21]
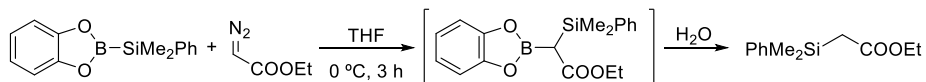
Scheme 4.13. Insertion of ethyl diazoacetate into B-Si bond.

Another strategy to introduce a $-SiR_3$ moiety in the final product is to perform insertion reactions with trialkylsilyldiazomethane (R_3SiCHN_2) because after reaction, the SiR_3 functional unit is present in the product. For that reason, different examples of $(CH_3)_3SiCHN_2$ insertion into B-C bond have been reported.

It was reported that the products obtained from hydroboration of alkenes with catecholborane undergo insertion with an excess of trimethylsilyldiazomethane in THF at reflux during 12 hours (Scheme 4.14).[22]
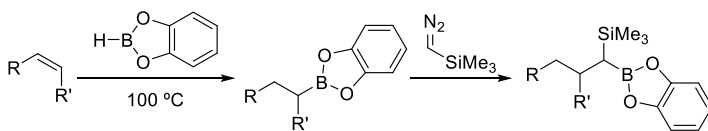
Scheme 4.14. Trimethylsilyldiazomethane insertion into C-B bond.

Me₃SiCHN₂ can also be inserted into a cyclic B-C bond of *B*-MeO-9-BBN, despite the fact that temperatures about 70 ºC are needed for achieving quantitative conversions of *B*-MeO-10-TMS-9-BBD (Scheme 4.15 a).[23] Also, it has been described that catecholborane derivatives can react with an excess of $(CH_3)_3SiCHN_2$ to generate α-borylsilanes in high yields (Scheme 4.15 b).[13]
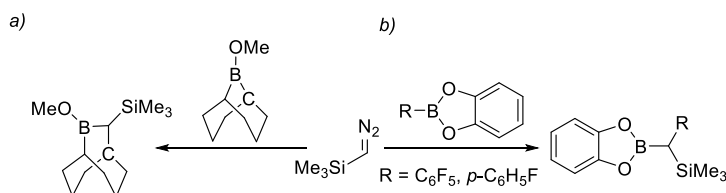
Scheme 4.15. Me₃SiCHN₂ insertion into B-C bond to generate α-borylsilanes.

The diazo compounds with no electro-withdrawing substituents, such as diazoalkanes and arylsubstituted diazomethane derivatives, are generally unstable and difficult to handle. They can be prepared *in situ* by base promoted decomposition of tosylhydrazones.[24]

The tosylhydrazones are synthesized from the condensation reaction of tosylhydrazine with the corresponding ketone or aldehyde (Scheme 4.16). They have been used in many reported metal-catalyzed reactions[25] as cross-coupling reactions.[26] More interesting diazo compounds generated from decomposition of tosylhydrazones have been reactive in metal-free insertion into B-H and B-B bonds.[12]
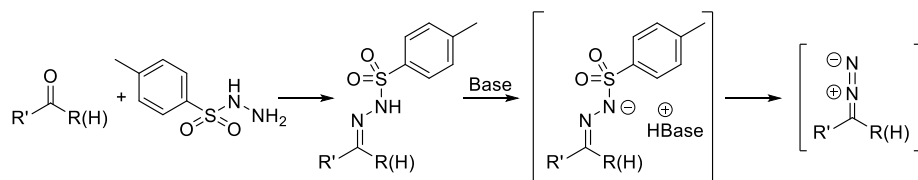
Scheme 4.16. Diazo compound generated from decomposition of tosylhydrazones

In 2012, Wang and co-workers reported the use of tosylhydrazones to react with bis(pinacolato)diboron and pinacolborane to generate new C-B bond.[27] When B_2pin_2 was used with the *in situ* generated diazo compound, which were obtained from aldehydes, the diazo compound was inserted into de B-B bond with concomitant protodeboronation of one Bpin moiety (Scheme 4.17 a). The reaction afforded the new C-B bond in moderated to high yields and was shown to be sensitive to steric hindrance in the diazo compound.

The desired products were obtained in high yields when less sterically demanding diazo compounds were inserted in less sterically demanding B-H bonds (Scheme 4.17 b).
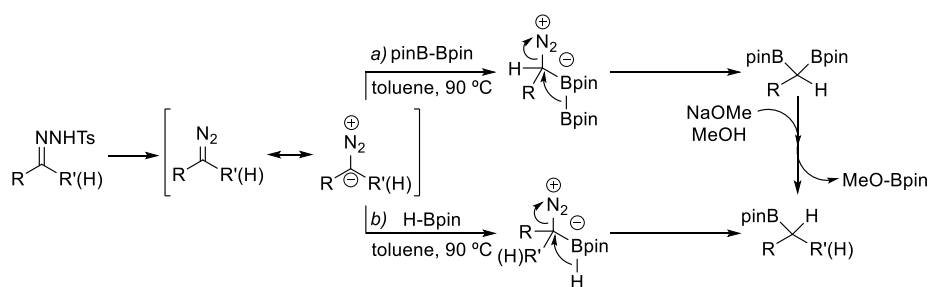
Scheme 4.17. Synthesis of new C-B from insertion of tosilhydrazones into B-B and B-H bonds.

Subsequently, the same group published the synthesis of 1,1-diborylalkanes and the synthesis of 1-boryl-1-silylalkanes through the reaction of tosylhydrazones with B_2pin_2 or pinB-SiMe$_2$Ph under transition metal free conditions.[28] They used a large variety of ketones and aldehydes to generate the tosylhydrazone, which in presence of sodium hydride formed the tosylhydrazone sodium salt and decomposed at 110 ºC to produce the diazo compound which react with bis(pinacolato)diboron and silylborane yielding the desired products in moderate to high yields (Scheme 4.18).

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations
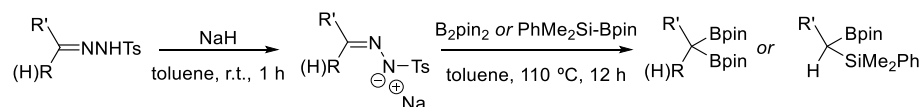
Scheme 4.18. Synthesis of 1,1-diborylalkanes and 1-boryl-1-silylalkanes through diazo compound insertion into B-B and B-Si bond.

More recently, our group, has experimentally proved the unsymmetrical 1,1-diboration of diazo compounds, formed *in situ* from aldehydes and cyclic and non-cyclic ketones, in the absence of any transition metal complex.[29]

The use of pinB-Bdan (dan = 1,8-diaminonaphthalene) for the synthesis of two geminal C–Pbin and C–Bdan bonds afforded the desired products in moderate to high yields (Scheme 4.19). Diastereoselection could be achieved for the substituted cyclic diazo compounds due to a combination of repulsive 1,3-diaxial and 1,2-*cis* interactions with the diboron reagent.
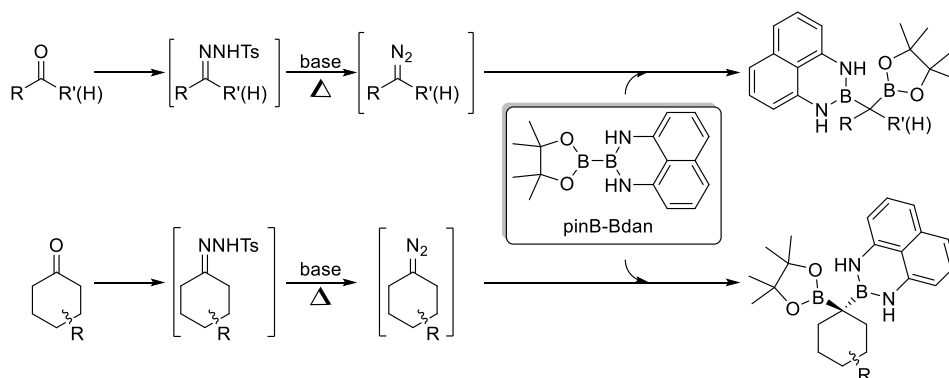
Scheme 4.19. Metal-free 1,1-diboration of an unsymmetrical pinB–Bdan diboron reagent to aldehydes and ketones, *via* diazo compounds.

4.2. Motivation

With all those precedents in mind and based on the previous work done in our group about the insertion of diazo compounds into the unsymmetrical B-B bond of pinB-Bdan, we became interested in the study of the insertion of diazo compounds into B-S bond.

In particular, we were interested to explore the insertion of trimethylsilyldiazomethane (**81**) into pinB-SPh (**1**) and pinB-SBn (**3**) reagents, to have access to the direct synthesis of main group, multisubstituted sp^3 carbons (Si, B, S). The concomitant functionalization of those HC(SR)(Bpin)(SiMe$_3$) compounds contribute to enhance the synthesis of structurally diverse molecules. We plan to perform deborylative alkylation, desilylation and deprotoalkylation (Scheme 4.20).
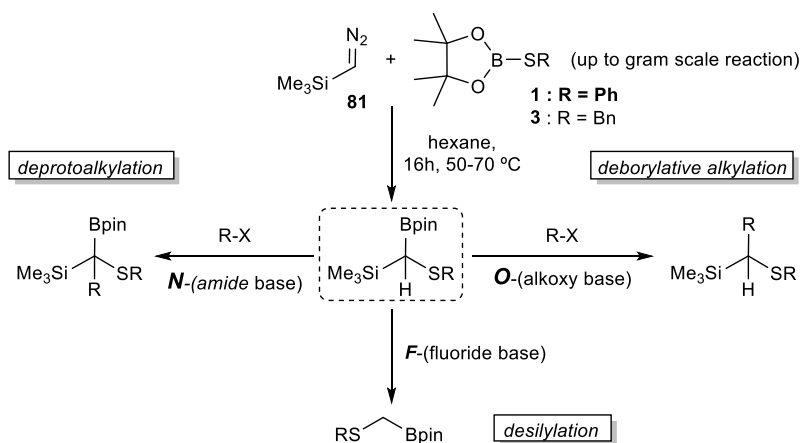
Scheme 4.20. Strategic trimethylsilyldiazomethane insertion into pinB-SR, followed by selective functionalizations.

4.3. Results and discussion

To verify experimentally the above hypothesis, we started the study by optimizing the insertion of the commercially available Me$_3$SiCHN$_2$ (**81**) with pinB-SPh (**1**).

Working in a 0.2 mmol scale, we decided to use 2 equivalents of **81** in the reaction with 1 equivalent of **1** to achieved full conversion of the inserted products.

When the reaction was performed at 50 °C during 16 hours, quantitative yield for HC(SPh)(Bpin)(SiMe$_3$) (**82**) was achieved but we found that decreasing the reaction time to 6 hours the conversion was not affected.

Then the reaction was also performed with pinB-SBn (**3**) to produce HC(SBn)(Bpin)(SiMe$_3$) (**83**) but higher temperatures and longer reaction times were needed to achieve full conversion (Scheme 4.21).
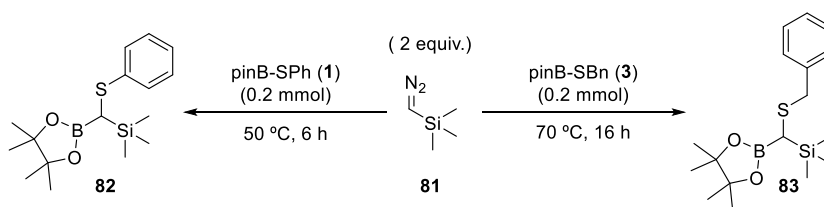
Scheme 4.21. Optimized reaction conditions for insertion of Me$_3$SiCHN$_2$ into pinB-SR.

In pinB-SPh (**1**) the lone pair of the sulfur has a double delocalization in the *p*-empty orbital of the boron atom and the π-system of the phenyl ring, but in the case of pinB-SBn (**3**), it has only the delocalization through the boron atom. This fact increases the occupancy of the *p*-orbital of the boron and consequently the B-S bond strength, this is in agreement with the more energetically demanding reaction conditions for the insertion of trimethylsilyldiazomethane (**81**) into the B-S bond of **3** than into the B-S bond of **1**.

The mechanism or the insertion of Me$_3$SiCHN$_2$ (**81**) into the B-S σ-bond, might be understood as an initial interaction of the nucleophilic diazo carbon to the electron deficient boron atom in pinB-SR. This might be followed by a 1,2-migration of the SR moiety to afford the α,α-substituted product and the concomitant release of dinitrogen (Scheme 4.22).

A similar mechanism was already postulated by DFT calculations using pinB-Bpin or pinB-Bdan and CH_3CHN_2 as the model diazoalkane, suggesting a concerted, yet asynchronous mechanism.[29]

diazo-boron coordination   Concerted-asynchronous
                                      transition state
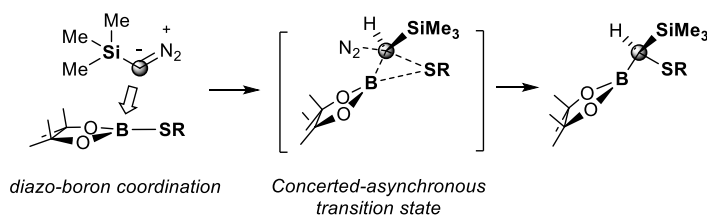
Scheme 4.22. Suggested mechanism for the insertion of Me_3SiCHN_2 into pinB-SR.

Interesting, it was possible to perform the insertion reaction in a gram scale achieving 95% isolated yield for **82** and 93% isolated yield for **83**. The main difference between the reactions carried out at 0.2 mmol scale and the ones carried out at gram scale was the nitrogen elution, for that reason the scaled-up reactions were carried out in a screw-cap Schlenck reaction tube to control the overpressure inside the reaction flask.

The empty *p*-orbital of the boron moiety is responsible of the Lewis acidity of the pinB-SR reagent and allows the insertion reaction and also might induce deborylative alkylation sequence from products **82** and **83**. Due to the high oxophilicity of the boron atom the sodium *tert*-butoxide base was selected to promote the alkoxide-induced deborylation, as described for the generation of α-boryl carbanions from germinal (bis)boronates.[30] Alkyl halides were selected as the electrophilic alkylating reagent because halides are good leaving groups. Reagent **82** and 1-bromotetradecane (**84**) were used as model reagents to establish the alkylation reaction. The optimized reaction conditions required 1 equivalent of the $^nC_{14}H_{29}Br$ with an excess of **82** (1.3 equiv.) in THF. An excess of **82** versus the alkyl halide was used to discard any plausible decomposition along the reaction.

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

Within 3 h, at room temperature, the α-silyl sulfide **85** was observed in 84% yield (Table 4.1, entry 1). Longer reaction times did not provide any higher conversions.

Table 4.1. Substrate scope of deborylative alkylation of **82**[a]
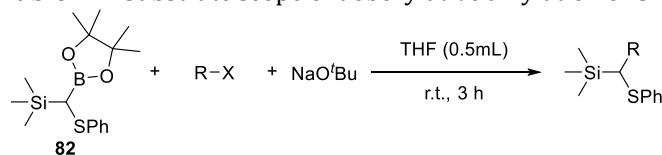
Entry	Substrate		Product		NMR Yield (%)[b]	Isolated Yield [%]
1	$^nC_{14}H_{29}Br$	**84**	Me_3Si—$^nC_{14}H_{29}$ / SPh	**85**	84	65
2	$^nC_{14}H_{29}Br$	**86**	Me_3Si—$^nC_4H_9$ / SPh	**87**	69	56
3	Br⌒⌒F **88**		Me_3Si⌒⌒⌒F / SPh	**89**	84	81
4	Br⌒⌒Cl **90**		Me_3Si⌒⌒⌒Cl / SPh	**91**	73	71
5	Cl⌒⌒Ph **92**		Me_3Si⌒═⌒Ph / SPh	**93**	80	74
6	Br⌒⌇ **94**		Me_3Si⌒⌇ / SPh	**95**	85	78
7	Br⌒Ph **96**		Me_3Si⌒Ph / SPh	**97**	80	75
8	Br⌒≡⌒ **98**		Me_3Si⌒≡⌒ / SPh	**99**	67	61
9	$(CH_2=CH)C_8H_{16}Br$ **100**		Me_3Si—$^nC_8H_{16}(CH=CH_2)$ / SPh	**101**	71	67
10	Br⌒△O **102**		Me_3Si⌒△O / SPh	**103**	81	-
11	I� **104**		Me_3Si⌒branched / SPh	**105**	71	68
12	Ph / Br⌒Ph **106**		Me_3Si—(Ph)(Ph) / SPh	**107**	40	15

[a]Reaction conditions: R–X (0.077 mmol), HC(Bpin)(SiMe₃)(SR) (1.3 equiv.), NaO^tBu (4 equiv.), THF (0.5 mL), at r.t. for 3 h. [b]Yields were determined by ¹H NMR analysis of the crude reaction mixture with 1,4-dinitrobenzene or naphthalene as an internal standard, which were added after the reaction.

102

When a less sterically hindered alkyl bromide was used, as 1-bromobutane (**86**), the deborylative alkylation took place in 69% yield of the corresponding α-silyl sulfides **87** (Table 4.1, entry 2). After that, we wanted to compare the leaving group ability of Br in front of Cl and F. For that reason, we conducted the reaction with 1-bromo-4-fluorobutane (**88**) and 1-bromo-4-chlorobutane (**90**) with reagent **82** and interesting the deborylative alkylation took place on the C-Br bond to generate 84% of **89** and 73% of **91**. In both cases the new C-C bond was formed selectively at the C-Br site, leaving the C-F and the C-Cl bonds intact (Table 4.1, entries 3 and 4). The bromine atom is a better leaving group because its high atomic radius stabilizes better the negative charge.

Alternativelly, the alkylation of cinnamyl chloride (**92**) was performed to generate the S_N2-type product (E)-trimethyl(4-phenyl-1-(phenylthio)but-3-en-1-yl)silane (**93**) in 80% yield. In this case, the reaction of the less reactive C-Cl bond took place due to the transition state stabilization through the conjugate system, the partial positive charge generated in the carbon bearing the halogen is stabilized by the double bond conjugated to the phenyl ring (Table 4.1, entry 5).

Other substrates with the ability of give extra stabilization in the transition state, as the ones bearing the bromine in allylic, benzylic or propargylic position as 3-bromo-2-methylprop-1-ene (**94**), (bromomethyl)benzene (**96**) and 1-bromopent-2-yne (**98**) respectivelly, afforded the corresponding α-silyl sulfides **95,97** and **99** in high yields (Table 4.1, entries 6-8).

The compatibility of other functional groups with respect to the base-mediated deborylative alkylation was demonstrated with a substrate bearing a terminal double bond in the carbon chain, substrate 10-bromodec-1-ene (**100**).

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

In this case, the corresponding product trimethyl(1-(phenylthio)undec-10-en-1-yl)silane (**101**) was nicely formed without any interaction of **81** effect to the unsaturated bond (

Table **4.1**, entry 9). Even more notable is the example where the substrate contains an epoxide ring, 2-(bromomethyl)oxirane (**102**), that remained untouched after the deborylative alkylation affording product **103** in high yields, but unfortunately was not possible to isolate it due to its decomposition during purification protocol (Table 4.1, entry 10).

More challenging substrates, as secondary alkyl halides, were used in the deborylative alkylation. We expected a decrease of the conversion because this kind of substitutions are affected by steric hindrance around the halogen.

In the case of diisopropyl iodide (**104**), the decrease of reactivity due to the steric hindrance is balanced with the better leaving group ability of the iodide, the reaction afforded trimethyl(2-methyl-1-(phenylthio)propyl)silane **105** in 71% yield (Table 4.1, entry 11). The use of more sterically hindered secondary alkyl electrophile, such as diphenylbromomethane (**106**) afforded the germinal thiosilane product (2,2-diphenyl-1-(phenylthio)ethyl)trimethylsilane (**107**) in 40% yield (Table 4.1, entry 12). This demonstrated that the deborylative alkylation of compound **82** tolerated a broad substrate scope, even for the most challenging electronic and steric secondary alkyl halides.

This two-step insertion/deborylative alkylation methodology constitute an unprecedented protocol for the synthesis of α-silyl sulfides.

When the deborylative alkylation was performed between HC(SBn)(Bpin)(SiMe$_3$) (**83**) and 1-bromotetradecane (**84**) as electrophile, with NaO^{t}Bu as base, a mixture of products was detected in the crude of the reaction.

104

It was possible identify three different products in the reaction media. The protodeboronated specie from **83** was detected in 11% yield (**108**), the desired alkylated product was detected in 20% yield (**109**) and a constitutional isomer of the α-silyl sulfide (**110**) in 40%. The similar polarity of the products **108** and **109** hampered its proper isolation from the reaction media.
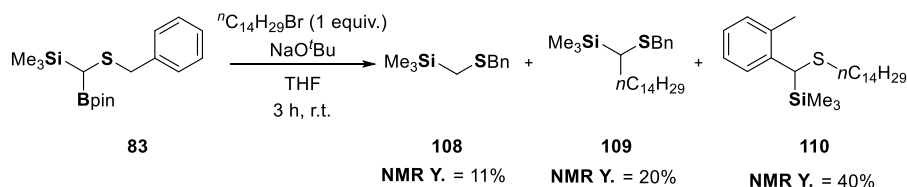
Scheme 4.23. Deborylative alkylation of **83** with 1-bromotetradecane (**84**) and NaO^{t}Bu.

Neither by increasing not decreasing the equivalents of base the reaction became cleaner. When we used sodium methoxide, as base the formation of ((benzylthio)methyl)trimethylsilane (**108**) was favored up to 88% yield (60% isolated yield). This can be explained with the better ability of methoxide to interact with the boron due to the less steric hindrance around the oxygen of the base.

The formation of the unexpected compound **110** could be explained as a result of a thia-Somelet-Haüser rearrangement. In this kind of processes an intramolecular [2,3]-sigmatropic rearrangement of sulfonium salt to *ortho*-substituted benzyl sulfides by means of the treatment with strong base could take place.[31]   Suggested mechanism to understand the formation of compound **110** is shown in Scheme 4.24. When the reagent **83** reacts with the base a borate complex (**D**) is formed. This complex can follow two different pathways: if the Bpin moiety is eliminated, the anion **E** is form and can be alkylate with the electrophile to form product **109** troughout deborylative alkylation.

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

If the lone pair of the sulfur attacks the electrophile in the intermediate **D** the betaine **F** is formed which can rearrange to form **110** or loss the Bpin moiety to form the ylide **G,** which can also rearrange to form **110.**
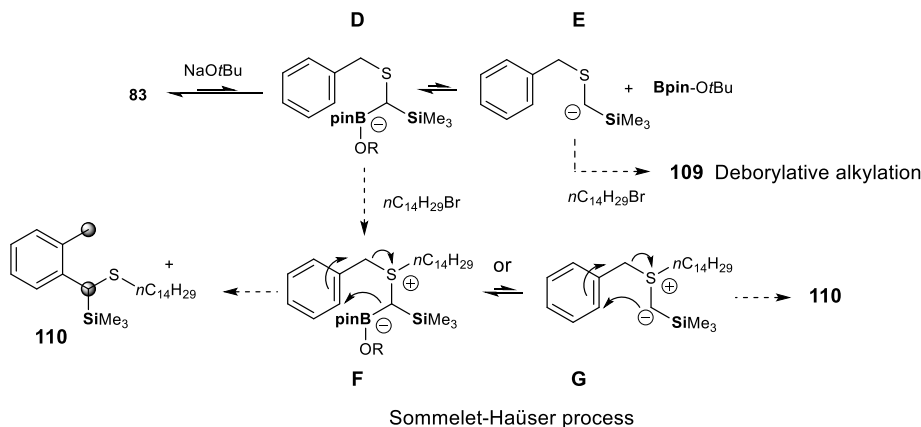
Scheme 4.24. Tentative suggestion to the formation of compound **109** or **110**.

To study the possibility of the formation of product **110** from the ylide **G** a blank experiment from **108** was carried out under the same reaction conditions. Our work hypothesis was that product **108,** obtained from the protodeboronation of **83** with NaOMe, can undergo a possible thia-Sommelet-Haüser rearrangement as is shown in Scheme 4.25. The sulfonium salt **H**, generated from alkylation in the sulfur atom of **108** by interaction of its lone pair and the alkyl halide $^{n}C_{14}H_{29}Br$, can interact with the base to generate the sulfur ylide than can rearrange to form the product **110**.
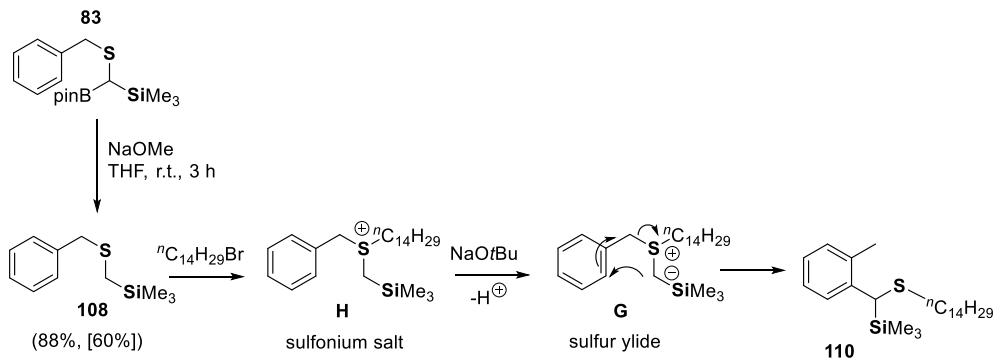
Scheme 4.25. Possible thia-Sommelet-Haüser rearrangement from **108.**

106

Experimentally, when we exposed compound **108** with 1-bromotetradecane (**84**) in the presence of 4 equivalents of NaO^{t}Bu at room temperature for 3 hours, the substrate was unaltered (Scheme 4.26). This blank reaction proved that the formation of compound **110** cannot go through **108** and might require the presence of the borate complex **A** to generate the betaine **C** which after rearrangement produces **110**.
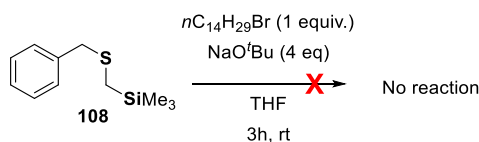
Scheme 4.26. Deborylative alkylation applied to **108** as a blank reaction.

Another functionalization that we also explored was the desilylative alkylation of compound **83** with the model alkylating reagent 1-bromotetradecane (**84**) in the presence of TBAF (4 equivalents), due to the high affinity of silicon atom with fluorides. After stirring for 1.5 hours complete conversion towards the protodesilylated product **111** (85% NMR yield, 67% isolated yiled) was observed with no detection of the alkylated product. No surprisingly, the same reaction outcome was observed in the absence of the electrophile ^{n}C$_{14}$H$_{29}$Br, with no effect on the yield. When the reaction was performed with substrate **81** the protodesilylated product **112** was formed in 66% isolated yield (Scheme 4.27).
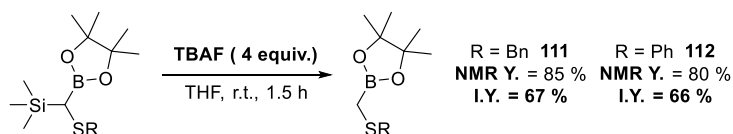
Scheme 4.27. Desilylation of **83** and **82** to afford **111** and **112**.

The possible explanation to justify thaht the desilylation took place instead of the desilylative alkylation can be related to the extra stabilization that the *p*-empty orbital of the boron gives to the anion that is generated *in situ*, which cannot be alkylated but it is protonated after work up.

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

Next, we turned our attention to the S_N2 alkylations that involve α-boron and α-silyl stabilized carbanions generated through deprotonation of **81**. When we used lithium 2,2,6,6-tetramethylpiperazine (LTMP)[32] and cinnamyl chloride **92** compound **113** was formed up to 70% isolated yield. The reaction with benzyl bromide **96** was also possible affording product **114** in moderate isolated yield.
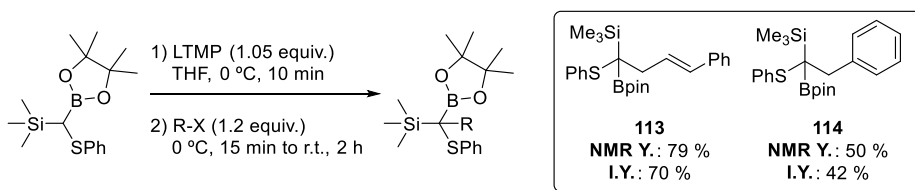
Scheme 4.28. Deprotonation followed by alkylation of substrate **82.**

This deprotonation alkylation methodology is a straightforward tool to synthesize high functionalized products. The scope of the reaction of $HC(SR)(Bpin)(SiMe_3)$ with LTMP and different alkyl halides was done by my co-worker Jordi Royes. He also studied a concomitat functionalization of the highly-functionalized products **115** and **116** (Figure 4.1), synthesized through the LTMP protocol, through highly-functionalized products.[33]
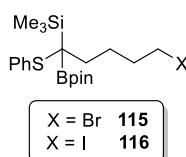
Figure 4.1. Highly-functionalized products used for further functionalization.

108

4.4. Conclusions

The trimethylsilyldiazomethane insertion into the B-S σ-bond of pinB-SPh (**1**) and pinB-SBn (**3**) has been achieved in quantitative yields even in a gram scale. The HC(SR)(Bpin)(SiMe$_3$) products have been further functionalized.

The deborylative alkylation of HC(SPh)(Bpin)(SiMe$_3$) (**82**), *via* NaO*t*Bu, can be performed with a wide scope of alkyl halides.

The deborylative alkylation of compound **83**, produced a rearranged product **110** probably formed via a Sommelet-Haüser process.

When using TBAF as a base the desilylation of the inserted products I favored, while the use of LTMP facilitates the deprotonation/alkylation of the α-boron, α-silyl stabilized carbanion.

Chapter 4

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

4.5. References

1 a) X. Xu, M. P. Doyle, *Acc. Chem. Res.* **2014**, *47*, 1396–1405; b) L. Liu, J. Zhang, *Chem. Soc. Rev.* **2016**,*45*, 506-516; c) H. M. L. Davies, J. Du Bois, J.-Q. Yu; *Chem. Soc. Rev.* **2011**,*40*, 1857-1869; d) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247; e) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377; f) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

2 N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937–2981.

3 Y. Zheng, R. Bian, X. Zhang, R. Yao, L. Qiu, X. Bao, X. Xu, *Eur. J. Org. Chem.* **2016**, *22*, 3872-3877.

4 A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341–2372.

5 a) J.-X. Guo, T. Zhou, B. Xu, S.-F. Zhu, Q.-L. Zhou, *Chem. Sci.* **2016**,*7*, 1104-1108; b) Y. Liu, Z. Yu, J. Z. Zhang, L. Liu, F. Xia, J. Zhang, *Chem. Sci.* **2016**,*7*, 1988-1995; c) M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, *Chem. Commun.*, **2016**, *52*, 7326-7335; d) G. Qin, L. Li, J. Li, H. Huang, *J. Am. Chem. Soc.* **2015**, *137*, 12490–12493; e) J. Pospech, A. J. J. Lennox, M. Beller, *Chem. Commun.* **2015**, *51*, 14505-14508; f) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; g) A. Caballero, E. Despagnet-Ayoub, M. M. Díaz-Requejo, A. Díaz-Rodríguez, M. E. González-Núñez, R. Mello, B. K. Muñoz, W. Solo Ojo, G. Asensio, M. Etienne, P. J. Pérez, *Science* **2011**, *332*, 835-838.

6 a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.*, **2003**, *103*, 2861–2904; b) M. M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, P. J. Pérez, *Dalton Trans.* **2006**, 5559-5566; c) M. M. Díaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379–3394; d) C.-Y. Zhou, J.-S. Huang, C.-M. Che, *Synlett* **2010,** *18,* 2681-2700; e) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

7 J. Pospech, A. J. J. Lennox, M. Bellera, *Chem. Commun.* **2015**, *51*, 14505-14508.

8 Y.-Z. Zhang, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 8496 –8498.

9 M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Angew. Chem. Int. Ed.* **2005**, *44*, 5284 –5288.

10 J. Tao, R. Tran, G. K. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 16312-16315.

11 S. R. Hansen, J. E. Spangler, J. H. Hansen, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 4626–4629.

12 H. Li, Y. Zhang, J. Wang, *Synthesis* **2013**, *45*, 3090-3098.

13 R. C. Neu, C. Jiang, D. W. Stephan, *Dalton Trans.* **2013**, *42*, 726-736.

14 D. Chen, X. Zhang, W. -Y. Qi, B. Xu, M. -H. Xu, *J. Am. Chem. Soc.* **2015**, *137*, 5268–5271.

15 X. Li, D. P. Curran, *J. Am. Chem. Soc.* **2013**, *135*, 12076–12081.

16 Q.-Q. Cheng, S.-F. Zhu, Y.-Z. Zhang, X.-L. Xie, Q.-L. Zhou, *J. Am. Chem. Soc.* **2013**, *135*, 14094–14097.

17 H. A. Ali, I. Goldberg, M. Srebnik, *Organometallics* **2001**, *20*, 3962-3965.

18 H. A. Ali, I. Goldberg, D. Kaufmann, C. Burmeister, M. Srebnik, *Organometallics* **2002**, *21*, 1870-1876.

19 A.J. Wommacka, J. S. Kingsbury, *Tetrahedron Lett.* **2014**, *55*, 3163–3166.

20 a) K. Endo, T. Ohkubo, M. Hirokami, T. Shibata, *J. Am. Chem. Soc.* **2010**, *132*, 11033–11035; b) K. Endo, T. Ohkubo, T. Shibata, *Org. Lett.* **2011**, *13*, 3368–3371; c) K. Endo, T. Ohkubo, T. Ishioka, T. Shibata, *J. Org. Chem.* **2012**, *77*, 4826–4831.

21 J. D. Buynak, B. Geng, *Organometallics* **1995**, *14*, 3112-3115.

22 J.-P. Goddard, T. Le Gall, C. Mioskowski, *Org. Lett.* **2000**, *2*, 1455–1456.

23 C. H. Burgos, E. Canales, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 8044-8049.

24 W. R. Bamford, T. S. Steven, *J. Chem. Soc.* **1952**, 4735-4740.

25 J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, *8*, 1479-1492.

26 a) J. Barluenga, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560–572; c) Q. Xiao, Y. Zhang, J. Wang, *Accounts Chem. Res.* **2013**, *46*, 236-247.

27 H. Li, L. Wang, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 2943 –2946.

28 H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang, J. Wang, *Org. Lett.* **2014**, *16*, 448–451.

Chapter 4

4. 1,1-Addition of pinB-SR to trimethylsilyl diazomethane followed by selective alkylations

29   A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó, E. Fernández, *Org. Biomol. Chem.* **2015**, *13*, 9659-9664.

30   K. Hong, X. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 10581–10584.

31   T. Tanzawa, N. Shirai, Y. Sato, K. Hatano, Y. Kurono, *J. Chem. Soc. Perkin Trans.* **1995**, 2845-2848.

32   K. Endo, M. Hirokami, T. Shibata, *J. Org. Chem.* **2010**, *75*, 3469–3472.

33   M. G. Civit, J. Royes, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernández, *Org. Lett.* **2016**, *18*, 3830–3833.

112

"I have always believed:

That if there is the right spirit,

we can kick out the "im" from "impossible""

Sir. Robert Baden-Powell

Chapter 5

Conclusions

5.1. *Chapter 2.* 1,4-Addition of pinB-SR to activated olefins

In this chapter, we have reported the direct synthesis of β-sulfido carbonyl compounds through thioboration/protonation methodology. The reaction between activated olefins and thiodioxaborolanes pinB-SPh, pinB-STol and pinB-SBn afforded the 1,4-addition products in moderate to good isolated yields.

A wide substrate scope is tolerated including cyclic and acyclic α,β-unsaturated ketones and aldehydes. Substrates can have bonded to the β-position alkyl or aryl substituents with electron-donating or electron-withdrawing groups.

The reaction take place at room temperature in THF with no need of any catalyst, additive or base. By the simple activation of the Bpin moiety with the carbonyl group the new C-S bond is created in 15 reported examples.

After the thioboration, 1,4-addition and 1,2-addition intermediates have been detected in the reaction crude. Its formation depends on the nature of the substrate where acyclic ketones lead to 1,4-addition intermediates, unsaturated aldehydes lead to the 1,2-addition intermediate and the cyclic ketones lead to a mixture of both intermediates.

In the protonation with methanol the intermediates are converted in the β-sulfido carbonyl compounds. The desired compounds are isolated in moderate to good yields

Chapter 5

5. Conclusions

5.2. *Chapter 3.* 1,4-Addition of pinB-SR and pinB-SeR to ynones

We have developed a methodology for the synthesis of stereodefined *Z*-vinyl sulfides and *Z*-vinyl selenides taking advantage of the powerful "pull-push" properties of the Bpin unit in the selenodioxaborolane reagent pinB-SeBPh and the thiodioxaborolanes reagents pinB-SPh and pinB-SBn.

Ynones reacts with chalcogenoboranes at 50 ºC in a metal free context without any additive except MeOH as solvent. The reaction scope includes methyl and aryl ketones bearing alkyl or aryl substituents in the *β*-position. The *Z*-alkenyl sulfides and selenides are synthetized quantitatively and isolated in moderate to good yields.

The high stereoselectivity towards the *Z*-isomer, in some examples being the *Z*-isomer the unique product formed, can be justify with the mechanistic proposal. The carbonyl group interacts with the *p*-empty orbital of the RY-Bpin (Y = Se or S and R = Ph or Bn), the RY moiety gain nucleophilicity and attacks the *β*-position of the ynone. This "face to face" mechanism leads the RY and the carbonyl group in the same side of the double bond.

The use of *α,β*-unsaturated esters in the reaction with selenodioxoborolanes also afforded the *Z*-vinyl selenides in moderate to good yields and with high stereoselectivity towards the *Z*-isomer following a similar mechanism as the reported for the ynones.

When the reaction is carried out in the presence of a phosphine the *anti*-3,4-selenoborated product is observed. The generation of a zwitterionic phosphonium allenolate is the responsible for the different outcome in the reactivity. After protodeboronation the *α*-phenylselenated compound is generated.

116

5.3. *Chapter 4.* 1,1-Addition of pinB-SR to trimethylsilyldiazomethane followed by selective alkylations

We successfully extended the use of thiodioxoborolanes pinB-SPh and pinB-SBn in the insertion of trimethylsilyldiazomethane in the B-S σ-bond. The reaction take place in mild reaction conditions and can be scaled up to gram scale affording the HC(SR)(Bpin)(SiMe$_3$) in high isolated yields.

The different properties of the carbon substituents allow the further functionalization of the molecule through selective processes as deborylative alkylation, desilylation and deprotoalkylation.

By using sodium *tert*-butoxide the Bpin moiety of the HC(SPh)(Bpin)(SiMe$_3$) can be replaced by an alkyl chain. The have been used a wide variety of primary alkyl halides bearing unsaturated carbons and different functional groups, also secondary alkyl halides have been used. A family of 12 HC(SPh)(R)(SiMe$_3$) products have been synthetized in moderate to god yields. The reaction with HC(SBn)(Bpin)(SiMe$_3$) afforded a rearranged product that can be formed through a Sommelet–Haüser process.

The use of a fluorinated base as TBAF introduced a proton in the position where the silicon atom was in moderated isolated yields. In the presence of alkyl halides was not possible to alkylate in the silicon position under this reaction conditions.

A bulkier nitrogenated base as LiTMP can abstract the proton with no effect on the boron and silicon atom generating a carbanion that can be alkylated. If a dihalogenated chain is used further deborylative alkylation and desilylative alkylation can be carried out to afford cyclic products.

Chapter 5

117

118

"Estimem el treball i volem

fer bé les coses"

Llei Escolta i Guia

Chapter 6

Experimental Part

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

6.1. General Information

Solvents and reagents: They were obtained from commercial suppliers and dried and/or purified (if needed) by standard procedures, as specified in "Purification of Laboratory Chemicals".[1] Dry dichloromethane (DCM) supplied by PANREAC was purified in a MBRAUN MB-SPS-800 solvent purification system before use. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl. Dry methanol was distilled over calcium hydride under an argon atmosphere. Boranes utilized, phenylsulphur pinacolborane (pinB-SPh), tolylsulphur pinacolborane (pinB-STol) and benzylsulphur pinacolborane (pinB-SBn), phenylselenium pinacolborane (pinB-SePh), were synthetized in the laboratory of Prof. Stephen A. Westcott at Mount Allison University, Sackville, NB (Canada).[2] All reactions were conducted in oven and flame-dried glassware under an inert atmosphere of argon, using Schlenk-type techniques.

Flash chromatography was performed on standard silica gel (Merck Kieselgel 60 F254 400-630 mesh). *Thin layer chromatography* was performed on Merck Kieselgel 60 F254 which was developed using standard visualizing agents: UV fluorescence (254 and 366 nm) or potassium permanganate/Δ.

NMR spectra were recorded at a Varian Goku 400 or a Varian Mercury 400 spectrometer. ^{1}H NMR and ^{13}C$\{^1$H$\}$ NMR chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: 7.26 ppm (^{1}H)) and (CDCl$_3$: 77.16 ppm (^{13}C)). ^{11}B$\{^1$H$\}$ NMR chemical shifts (δ) are reported in ppm relative to (CH$_3$)$_2$O$\cdots$BF$_3$. ^{29}Si$\{^1$H$\}$ NMR chemical shifts (δ) are reported in ppm relative to (CH$_3$)$_4$Si. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptuplet, br = broad, m = multiplet), coupling constants (Hz) and integration.

6. Experimental Part

High resolution mass spectra (HRMS) were recorded using a 6210 Time of Flight (TOF) mass spectrometer from Agilent Technologies (Waldbronn, Germany) with an ESI interface and it was performed at the Servei de Recursos Científics i Tècnics (Universitat Rovira I Virgili, Tarragona) or using a BIOTOF II Time of Flight (TOF) mass spectrometer from Bruker with an APCI interface or EI interface and it was performed at the Unidade de Espectrometría de Masas e Proteómica (Universidade de Santiago de Compostela, Santiago de Compostela).

GC-MS analyses were performed on a HP6890 gas chromatograph and an Agilent Technologies 5973 Mass selective detector (Waldbronn, Germany) equipped with an achiral capillary column HP-5 (30m, 0.25mm i. d., 0.25μm thickness) using He as the carrier gas.

6.2. Experimental Procedures and spectral data
6.2.1. General procedure and spectral data of Chapter 2
Sulfonation of α,β-unsaturated ketones and aldehydes by pinB-SAr.
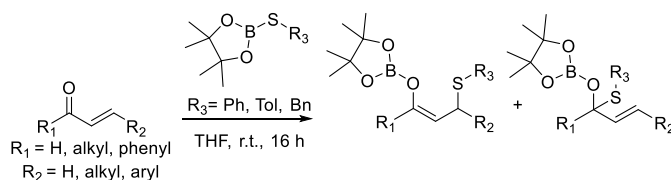
In the glove-box, an oven-dried Schlenk reaction tube equipped with a magnetic stir bar was charged with pinB-SPh (**1**), pinB-STol (**2**) or pinB-SBn (**3**) (1.1 equiv. - 4.5 equiv.). Then, the corresponding substrate (0.10 mmol) was added and all was dissolved in dry THF (2 mL). The mixture was stirred for 16 hours at room temperature. The solvent was evaporated to dryness and the crude residue was analyzed by ^{1}H NMR.

(Z)-4,4,5,5-tetramethyl-2-((4-phenyl-4-(phenylthio)but-2-en-2-yl)oxy)-1,3,2-dioxaborolane (Intermediate no isolated)

5b
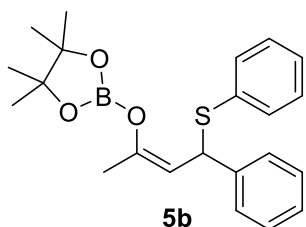
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 5.30 (d, J = 9.7 Hz, 1H), 5.03 (d, J = 9.7 Hz, 1H), 1.90 (s, 3H), 1.25 (s, 6H), 1.21 (s, 6H).

(Z)-2-((4-(4-methoxyphenyl)-4-(phenylthio)but-2-en-2-yl)oxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

6b
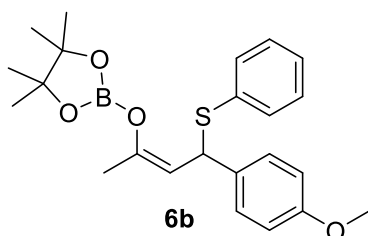
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 7.51–7.46 (m, 2H), 6.83–6.75 (m, 2H), 5.27 (d, *J* = 9.7 Hz, 1H), 5.00 (dq, *J* = 9.7, 1.0 Hz, 1H), 3.75 (s, 3H), 1.89 (d, *J* = 0.9 Hz, 3H), 1.24 (s, 6H), 1.21 (s, 6H). **¹H-¹³C 2D HSQC NMR of main signals** (400 MHz, CDCl₃) δ (ppm): 5.27-47.5 (CH), 5.00-111.7 (CH).

(Z)-2-((4-(4-chlorophenyl)-4-(phenylthio)but-2-en-2-yl)oxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

7b
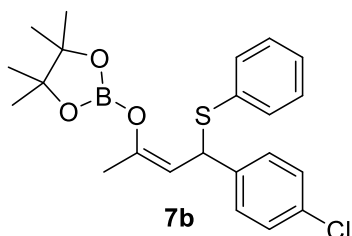
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 5.24 (d, J = 9.6 Hz, 1H), 4.96 (dq, J = 9.6, 1.0 Hz, 1H), 1.90 (d, J = 0.8 Hz, 3H), 1.24 (s, 6H), 1.21 (s, 6H).

6. Experimental Part

(Z)-2-((1,3-diphenyl-3-(phenylthio)prop-1-en-1-yl)oxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

8b
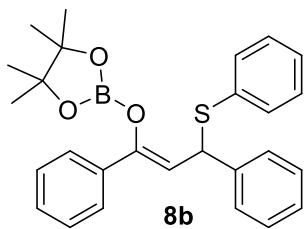
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 5.85 (d, J = 9.7 Hz, 1H), 5.42 (d, J = 9.7 Hz, 1H), 1.17 (s, 6H), 1.12 (s, J = 3.6 Hz, 6H). **¹H-¹³C 2D HSQC NMR of main signals** (400 MHz, CDCl₃) δ (ppm): 5.84-112.3 (CH), 5.42-48.8 (CH).

4,4,5,5-tetramethyl-2-((1-(phenylthio)cyclohex-2-en-1-yl)oxy)-1,3,2-dioxaborolane

9a
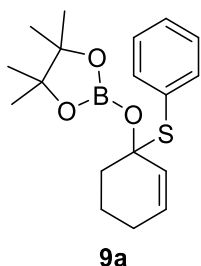
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 5.99–5.94 (m, 1H), 5.74 (dt, J = 10.2, 3.6 Hz, 1H). **¹H-¹³C 2D HSQC NMR of main signals** (400 MHz, CDCl₃) δ (ppm): 5.97-129.3 (CH), 5.74-129.2 (CH).

4,4,5,5-tetramethyl-2-((3-(phenylthio)cyclohex-1-en-1-yl)oxy)-1,3,2-dioxaborolane

9b
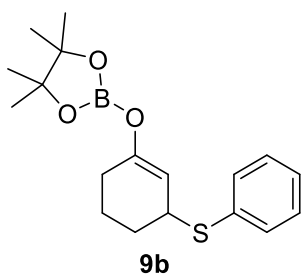
No isolated intermediate.

¹H NMR of main signals (400 MHz, CDCl₃) δ (ppm): 5.40 (dt, J = 4.4, 1.3 Hz, 1H, H_A), 3.99–3.93 (m, 1H, H_B). **¹H-¹³C 2D HSQC NMR of main signals** (400 MHz, CDCl₃) δ (ppm): 5.40-106.9 (CH), 3.95-44.0 (CH).

124

4,4,5,5-tetramethyl-2-((1-(phenylthio)but-2-en-1-yl)oxy)-1,3,2-dioxaborolane

10a
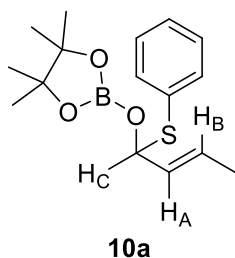
Intermediate no isolated

^{1}H NMR of main signals (400 MHz, CDCl$_3$) δ (ppm): 5.90–5.87 (m, 1H, H$_C$), 5.84–5.73 (m, 1H, H$_B$), 5.64–5.56 (m, 1H, H$_A$), 1.66-1.63 (m, 3H), 1.13 (s, 6H), 1.09 (s, 6H). **^{1}H-^{13}C 2D HSQC NMR of main signals** (400 MHz, CDCl$_3$) δ (ppm): 5.88-81.7 (CH), 5.77-128.0 (CH), 5.60-128.6 (CH).

Methanolysis of the 1,2-addition and 1,4-addition intermediates.

R_1 = H, alkyl, phenyl
R_2 = H, alkyl, aryl
R_3 = Ph, Tol, Bn
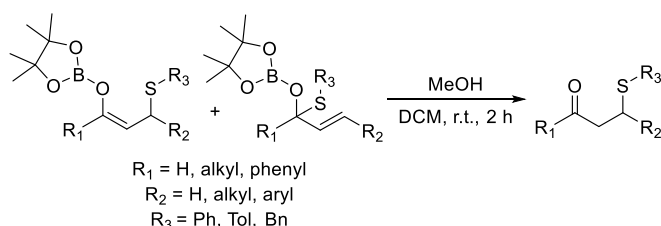
When the 1,2-addition or the 1,4-addition intermediates were detected by ^{1}H NMR, a methanolysis was carried out. The reaction was performed in 2 mL of dichloromethane (DCM) and an excess of MeOH (0.05 mL). The reaction was stirred for 2 hours at room temperature. The solvent was evaporated to dryness and the crude residue was analyzed by ^{1}H NMR. Then the *β*-thiolated products were purified by silica gel flash chromatography

4-phenyl-4-phenylthio-2-butanone

16
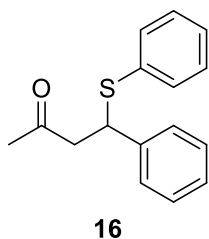
Yield for **16**: 16.4mg (64%) as a yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.31–7.25 (m, 6H), 7.25–7.18 (m, 4H), 4.71 (dd, *J* = 8.0, 6.6 Hz, 1H), 3.09 (dd, *J* = 16.2, 7.3 Hz, 1H), 3.03 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.08 (s, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 205.7, 141.1,

6. Experimental Part

134.1, 133.0, 129.0, 128.6, 127.8, 127.8, 127.6, 49.6, 48.1, 30.9. **HRMS** (ESI) for $C_{16}H_{16}NaOS$ [M+Na]+: calculated: 279.0820, found: 279.0809.

4-(4-methoxyphenyl)-4-phenylthio-2-butanone
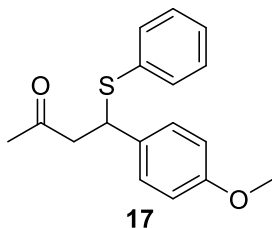
Yield for **17**: 20.0 mg (70%) as a yellowish solid.

1H NMR (400 MHz, CDCl$_3$) δ (ppm):7.31–7.16 (m, 7H), 6.81–6.76 (m, 2H), 4.68 (dd, J = 8.3, 6.4 Hz, 1H), 3.77 (s, 3H), 3.05 (dd, J = 17.0, 8.5 Hz, 1H), 2.99 (dd, J = 16.9, 6.5 Hz, 1H), 2.05 (s, 3H). **13C NMR** (100 MHz, CDCl$_3$) δ (ppm): 205.9, 158.9, 134.3, 133.0, 132.9, 129.0, 128.9, 127.6, 114.0, 55.4, 49.9, 47.6, 30.9. **HRMS** (ESI) for $C_{17}H_{18}NaO_2S$ [M+Na]+: calculated: 309.0925, found: 309.0927.

4-(4-chlorophenyl)-4-phenylthio-2-butanone
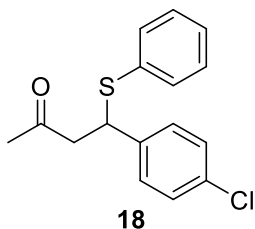
Yield for **18**: 21.8 mg (75%) as a yellowish solid.

1H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.31 – 7.18 (m, 9H), 4.69 (t, J = 7.3 Hz, 1H), 3.05 (d, J = 7.3 Hz, 2H), 2.10 (s, 3H). **13C NMR** (100 MHz, CDCl$_3$) δ (ppm): 205.3, 139.8, 133.6, 133.2, 133.2, 129.2, 129.1, 128.7, 128.0, 49.4, 47.5, 30.8. **HRMS** (ESI) for $C_{16}H_{15}ClNaO_2S$ [M+Na]+: calculated: 313.0430, found: 313.0429.

3-phenylthio-1-cyclohexanone [3]
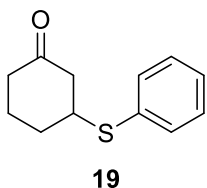
Yield for **19**: 14.4 mg (70%) as a yellowish oil.

1H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.45–7.40 (m, 2H), 7.34–7.27 (m, 3H), 3.43 (tdd, J = 10.4, 4.5, 3.4 Hz, 1H), 2.69 (ddt, J = 14.2, 4.4, 1.6 Hz, 1H), 2.41–2.26 (m, 3H), 2.21–2.09 (m, 2H), 1.80–1.64 (m, 2H). **13C NMR** (100 MHz, CDCl$_3$) δ (ppm): 208.9, 133.4, 133.1, 129.2, 127.9, 47.9, 46.3, 41.0, 31.4, 24.2.

126

HRMS (ESI) for $C_{12}H_{15}OS$ [M+H]$^+$: calculated: 207.0844, found: 207.0845. For $C_{12}H_{14}NaOS$ [M+Na]$^+$: calculated: 229.0663, found: 229.0663.

3-phenylthiobutanal
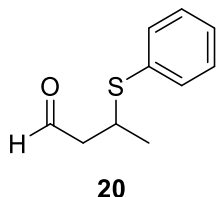
Yield for **20**: 14.4 mg (80%) as a yellowish oil.

¹H NMR (400 MHz, CDCl$_3$) δ (ppm): 9.76 (t, J = 1.7 Hz, 1H), 7.45–7.41 (m, 2H), 7.35–7.27 (m, 3H), 3.75–3.65 (m, 1H), 2.71 (ddd, J = 17.3, 6.0, 1.8 Hz, 1H), 2.59 (ddd, J = 17.3, 7.6, 1.7 Hz, 1H), 1.37–1.34 (m, 3H). **¹³C NMR** (100 MHz, CDCl$_3$) δ (ppm): 200.7, 137.8, 133.1, 129.2, 127.8, 50.2, 37.7, 21.3. **HRMS** (ESI) for $C_{10}H_{13}OS$ [M+H]$^+$: calculated: 181.0687, found: 181.0634.

1-phenyl-4-phenylthio-1-butanone
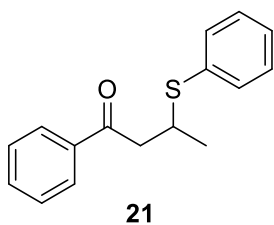
Yield for **21**: 18.5 mg (72%) as a yellowish oil.

¹H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.87-7.84 (m, 2H), 7.54–7.48 (m, 1H), 7.43–7.37 (m, 4H), 7.28–7.17 (m, 3H), 3.87 (dqd, J = 9.0, 6.7, 4.6 Hz, 1H), 3.25 (dd, J = 16.9, 4.5 Hz, 1H), 3.06 (dd, J = 16.9, 9.0 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H). **¹³C NMR** (100 MHz, CDCl$_3$) δ (ppm): 198.2, 136.9, 134.5, 133.4, 132.4, 129.1, 128.8, 128.2, 127.4, 45.6, 38.8, 21.1. **HRMS** (ESI) for $C_{16}H_{17}OS$ [M+H]$^+$: calculated: 257.1000, found: 257.0993. For $C_{16}H_{16}NaOS$ [M+Na]$^+$: calculated: 279.0820, found: 279.0812.

3-phenylthio-1-cyclopentanone
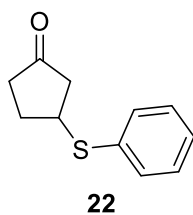
Yield for **22**: 15.0 mg (78%) as a yellowish oil.

¹H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.44–7.37 (m, 2H), 7.35–7.26 (m, 3H), 3.94–3.86 (m, 1H), 2.65–2.44 (m, 4H), 2.40–2.13 (m, 4H). **¹³C NMR** (100 MHz, CDCl$_3$) δ (ppm): 216.7, 134.4, 132.2, 129.3, 127.7, 45.4, 43.6, 37.0, 29.9.

HRMS (ESI) for $C_{11}H_{13}OS$ [M+H]$^+$: calculated: 193.0687, found: 193.0668.

6. Experimental Part

1-phenylthio-3-pentanone
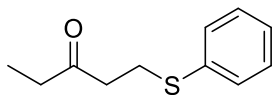
Yield for **23**: 15.7 mg (81%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.35–7.26 (m, 4H), 7.22–7.17 (m, 1H), 3.15 (t, J = 7.3 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.42 (q, J = 7.3 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 209.6, 135.9, 129.6, 129.2, 126.4, 41.9, 36.4, 27.7, 7.9. **HRMS** (ESI) for $C_{11}H_{15}OS$ [M+H]⁺: calculated: 195.0844, found: 195.0835.

4-phenylthio-2-heptanone [4]
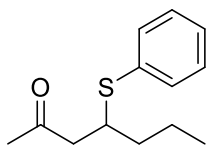
Yield for **24**: 17.8 mg (80%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.42–7.38 (m, 2H), 7.33–7.21 (m, 3H), 3.64–3.56 (m, 1H), 2.72 (dd, J = 17.2, 6.1 Hz, 1H), 2.63 (dd, J = 17.2, 7.4 Hz, 1H), 2.13 (s, 3H), 1.57–1.42 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 207.1, 134.6, 132.5, 129.1, 127.3, 49.3, 43.6, 37.1, 30.9, 20.3, 14.0. **HRMS** (ESI) for $C_{13}H_{19}OS$ [M+H]⁺: calculated: 223.1157, found: 223.1142. For $C_{13}H_{18}NaOS$ [M+Na]⁺: calculated: 245.0976, found: 245.0964.

4-phenylthio-2-nonanone
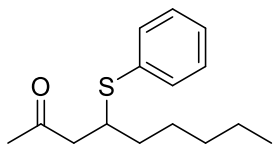
Yield for **25**: 17.7 mg (71%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.39–7.34 (m, 2H), 7.29–7.17 (m, 3H), 3.55 (m, 1H), 2.68 (dd, J = 17.2, 6.2 Hz, 1H), 2.60 (dd, J = 17.2, 7.4 Hz, 1H), 2.09 (s, 3H), 1.54–1.38 (m, 4H), 1.26–1.20 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 207.0, 134.7, 132.5, 129.1, 127.3, 49.3, 43.9, 34.9, 31.7, 30.8, 26.7, 22.7, 14.2. **HRMS** (ESI) for $C_{15}H_{23}OS$ [M+H]⁺: calculated: 251.1470, found: 251.1462. For $C_{15}H_{24}NaOS$ [M+Na]⁺: calculated: 273.1289, found: 273.1279.

128

5-benzylthio-3-hexanone [5]
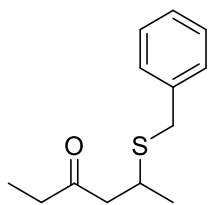
Yield for **27**: 12.2 mg (55%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.34–7.28 (m, 4H), 7.26–7.20 (m, 1H), 3.76 (s, 2H), 3.23–3.13 (m, 1H), 2.66 (dd, J = 16.6, 6.0 Hz, 1H), 2.50 (dd, J = 16.6, 8.0 Hz, 1H), 2.36 (qd, J = 7.3, 2.2 Hz, 2H), 1.26 (d, J = 6.7 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 209.4, 138.5, 128.9, 128.7, 127.2, 49.7, 36.7, 35.7, 35.2, 21.7, 7.8. **HRMS** (ESI) for $C_{13}H_{19}OS$ [M+H]⁺: calculated: 223.1157, found: 223.1153. For $C_{13}H_{18}NaOS$ [M+Na]⁺: calculated: 245.0976, found: 245.0971.

5-(p-tolylthio)hexan-3-one
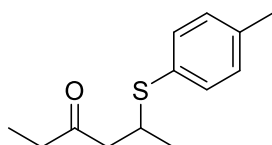
Yield for **29**: 13.5 mg (61%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.32 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.69–3.59 (m, 1H), 2.71 (dd, J = 16.8, 5.4 Hz, 1H), 2.51 (dd, J = 16.8, 8.5 Hz, 1H), 2.40 (qd, J = 7.3, 2.4 Hz, 2H), 2.33 (s, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 209.5, 137.7, 133.2, 130.5, 129.8, 49.3, 38.9, 36.8, 21.3, 21.2, 7.8. **HRMS** (ESI) for $C_{13}H_{19}OS$ [M+H]⁺: calculated: 223.1157, found: 223.1161.

4-benzylthio-2-nonanone [6]
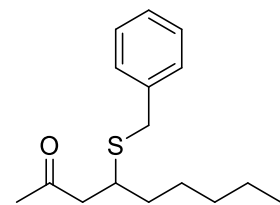
Yield for **30**: 8.0 mg (30%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.29–7.21 (m, 4H), 7.21–7.15 (m, 1H), 3.67 (d, J = 1.4 Hz, 2H), 2.98 (p, J = 6.8 Hz, 1H), 2.61 (dd, J = 16.8, 7.1 Hz, 1H), 2.53 (dd, J = 16.8, 6.7 Hz, 1H), 2.03 (s, 3H), 1.42 (dd, J = 7.6, 6.5 Hz, 2H), 1.31–1.17 (m, 6H), 0.80 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 207.1, 138.6, 129.0, 128.6, 127.1, 49.8, 40.5, 35.9, 35.2, 31.7, 30.7, 26.4, 22.7, 14.2.

6. Experimental Part

HRMS (ESI) for $C_{16}H_{25}OS$ [M+H]$^+$: calculated: 265.1626, found: 265.1623.

4-(p-tolylthio)nonan-2-one [7]

31
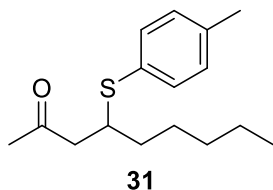
Yield for **31**: 19.8 mg (75%) as a yellowish oil.

¹H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.31 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 3.53–3.45 (m, 1H), 2.69 (dd, *J* = 17.0, 6.3 Hz, 1H), 2.59 (dd, *J* = 17.0, 7.4 Hz, 1H), 2.33 (s, 3H), 2.12 (s, 3H), 1.57–1.44 (m, 4H), 1.32–1.26 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H). **¹³C NMR** (100 MHz, CDCl$_3$) δ (ppm): 207.1, 137.6, 133.3, 130.6, 129.8, 49.3, 44.3, 34.8, 31.7, 30.8, 26.7, 22.7, 21.3, 14.2. **HRMS** (ESI) for $C_{16}H_{25}OS$ [M+H]$^+$: calculated: 265.1625, found: 265.1624.

6.2.3. General procedure and spectral data of Chapter 3

Synthesis of α,β-alkynyl ketones
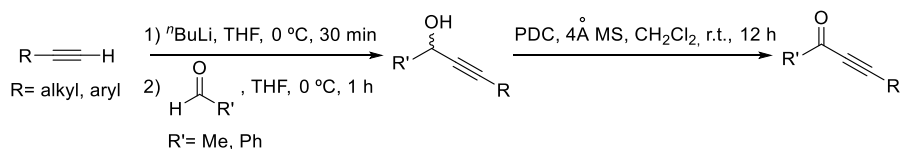
To a solution of distilled alkyne (8.5 mmol) in 5 mL of dry THF in an oven-dried Schlenk round-bottom flask at 0 ºC was added drop-wise *n*-butyllithium (1.6M in hexanes, 1 equiv.). After stirring for 30 min under argon, the corresponding aldehyde (1 equiv.) was added. After stirring for an additional 1 h, the reaction mixture was quenched by adding water (7 mL) and acidified by adding saturated NH$_4$Cl (3 mL). Then the mixture was extracted with ethyl acetate (2 x 6 mL) and finally with CH$_2$Cl$_2$ (6 mL). The combined organic layers were dried over MgSO$_4$ and filtered. After evaporation of the solvent, the crude alcohol product was obtained.

The crude alcohol product was dissolved in dry CH_2Cl_2 (5 mL) and added drop-wise over a period of 20 min to a suspension of pyridinium dichromate (1.5 equiv.) and 1.6 g of 4 Å molecular sieves in 12 mL of dry CH_2Cl_2 in an oven-dried Schlenk round-bottom flask. After stirring for 12 h, the reaction was diluted with 20 mL of diethyl ether and filtered through a plug of celite. The filtrated was evaporated and was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and diethyl ether adequate for each case.

4-(p-tolyl)but-3-yn-2-one[8]
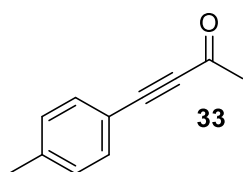
Yield for **33**: 1.2 g (87%) as a yellowish solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.45 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 184.8, 141.5, 133.2, 129.5, 116.8, 91.1, 88.2, 32.8, 21.8.

4-(4-(trifluoromethyl)phenyl)but-3-yn-2-one[9]
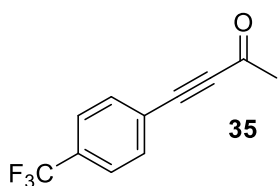
Yield for **35**: 2.2 g (81%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.67 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 2.47 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 184.3, 133.2, 132.2 (q, *J_{C-F}* = 32.9 Hz), 125.6 (q, *J_{C-F}* = 3.8 Hz), 123.8 (q, *J_{C-F}* = 1.2 Hz), 123.6 (q, *J_{C-F}* = 272.5 Hz), 89.4, 87.7, 32.8. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -63.20. **m.p.** 33.2 °C.

3-nonyn-2-one[10]
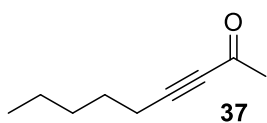
Yield for **37**: .975.0 mg (83%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.27 (t, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.56–1.44 (m, 2H), 1.34–1.20 (m, 4H), 0.82 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 184.7, 94.0, 81.3, 32.7, 30.9, 27.3, 22.0, 18.8, 13.8.

6. Experimental Part

1-phenyloct-2-yn-1-one[11]

39
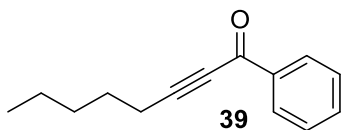
Yield for **39**: 1.5 g (88%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.15–8.11 (m, 2H), 7.60–7.55 (m, 1H), 7.48–7.43 (m, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.70–1.62 (m, 2H), 1.48–1.40 (m, 2H), 1.40–1.30 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 178.3, 136.9, 133.9, 129.6, 128.5, 97.0, 79.7, 31.2, 27.6, 22.2, 19.2, 14.0.

1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one[12]

41

F₃C
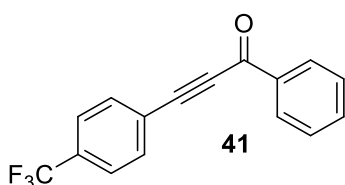
Yield for **41**: 1.8 g (79%) as a yellowish solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.22 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.71–7.64 (m, 3H), 7.57–7.52 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 177.8, 136.7, 134.6, 133.3, 132.4 (q, J_{C-F} = 33.0 Hz), 129.8, 128.9, 125.8 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 1.5 Hz), 123.7 (q, J_{C-F} = 272.5 Hz), 90.6, 88.2. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -63.14. **m.p.** 84.4 ºC.

1-phenyl-3-(p-tolyl)prop-2-yn-1-one[13]

43
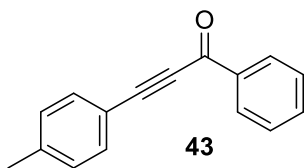
Yield for **43**: 1.7 g (90%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.23 (d, *J* = 7.1 Hz, 2H), 7.65–7.61 (m, 1H), 7.61–7.57 (m, 2H), 7.54–7.49 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 2.41 (s, *J* = 2.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 178.2, 141.7, 137.1, 134.2, 133.3, 129.7, 129.6, 128.7, 117.1, 94.0, 86.9, 22.0. **m.p.** 62 ºC.

132

β-selenation of α,β-alkynyl ketones

R= alkyl, phenyl
R'= alkyl, phenyl
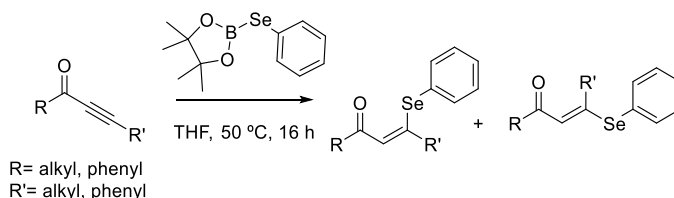
The reagent pinB-SePh (**4**) (2 equiv.) was weighted and transferred into an oven-dried Schlenk tube inside the glovebox. The corresponding substrate (0.10 mmol) was introduced in the Schlenk tube under argon and dry THF (2 mL) was added. The mixture was stirred for 16 hours at 50 ºC. After cooling down the reaction, the solvent was removed under vacuum and the resulting residue was analysed by ^{1}H NMR. Conversion and selectivity were determined by ^{1}H NMR. The product was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and ethyl acetate adequate for each case.

(Z)-4-phenyl-4-(phenylselanyl)but-3-en-2-one[14]
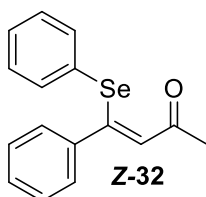
Yield for **Z-32**: 26.3 mg (87%) as a yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.23–7.19 (m, 2H), 7.10–6.96 (m, 8H), 6.81 (s, 1H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 196.8, 162.6, 139.3, 136.3, 129.9, 128.8, 128.4, 128.1, 128.0, 127.6, 124.4, 30.5. **HRMS** (ESI) for C$_{16}$H$_{15}$OSe [M+H]$^+$: calculated: 303.0288, found: 303.0290.

(Z)-4-(phenylselanyl)-4-(p-tolyl)but-3-en-2-one
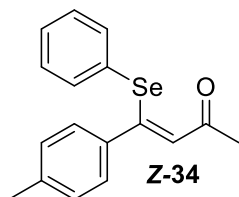
Yield for **Z-34**: 27.1 mg (86%) as a yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.21 (d, J = 6.9 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.99 (t, J = 7.4 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 7.9 Hz, 2H), 6.79 (s, 1H), 2.33 (s, 3H), 2.19 (s, 3H).

133

6. Experimental Part

13C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.6, 162.8, 138.2, 136.4, 136.1, 130.1, 128.8, 128.4, 128.2, 127.8, 124.3, 30.5, 21.2. **HRMS** (ESI) for C$_{17}$H$_{17}$OSe [M+H]$^+$: calculated: 317.0445, found: 317.0438; for C$_{17}$H$_{16}$NaOSe [M+Na]$^+$: calculated: 339.0264, found: 339.0264.

(Z)-4-(phenylselanyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one
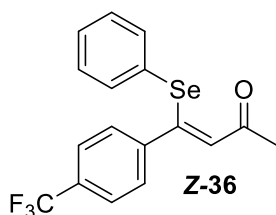
Yield for **Z-36**: 29.9 mg (81%) as a brown solid.

1H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.1, 2H), 7.10 (t, *J* = 8.7 Hz, 3H), 6.99 (t, *J* = 7.4 Hz, 2H), 6.81 (s, 1H), 2.36 (s, 3H).

13C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.7, 160.8, 142.8, 136.4, 123.0 (q, *J*$_{C-F}$ = 32.5 Hz), 129.2, 129.1, 128.7, 128.4, 124.6, 124.5 (q, *J*$_{C-F}$ = 3.8 Hz), 123.8 (q, *J*$_{C-F}$ *J* = 272.2 Hz), 30.6. **19F{1H} NMR** (377 MHz, CDCl$_3$) δ (ppm): -62.86. **m.p.** 81 °C. **HRMS** (ESI) for C$_{17}$H$_{14}$F$_3$OSe [M+H]$^+$: calculated: 317.0162, found: 317.0168

(Z)-4-(phenylselanyl)non-3-en-2-one[15]
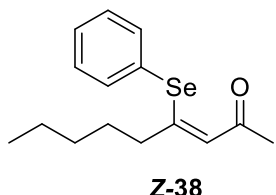
Yield for **Z-38**: 26.0 mg (88%) as a yellowish oil.

1H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.66 (d, *J* = 7.9 Hz, 2H), 7.43–7.38 (m, 1H), 7.36–7.32 (m, 2H), 6.68 (s, 1H), 2.25 (s, 3H), 2.20 (t, *J* = 7.7 Hz, 2H), 1.35–1.28 (m, 2H), 1.13–1.03 (m, 2H), 1.02–0.93 (m, 2H), 0.76 (t, *J* = 7.2 Hz, 3H). **13C NMR** (100 MHz, CDCl$_3$) δ (ppm): 196.8, 165.8, 137.5, 129.2, 129.1, 128.5, 121.6, 38.0, 31.2, 30.0, 29.9, 22.3, 14.0. **HRMS** (ESI) for C$_{15}$H$_{21}$OSe [M+H]$^+$: calculated: 297.0758, found: 297.0733; for C$_{17}$H$_{13}$NaOSe [M+Na]$^+$: calculated: 319.0577, found: 319.0552.

(Z)-1-phenyl-3-(phenylselanyl)oct-2-en-1-one
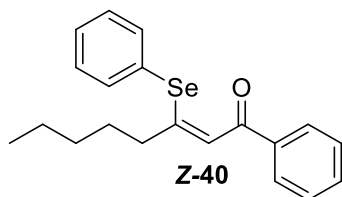
Yield for **Z-40**: 20.7 mg (58%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.03–7.99 (m, 2H), 7.73–7.69 (m, 2H), 7.57–7.52 (m, 1H), 7.50–7.40 (m, 4H), 7.40–7.34 (m, 2H), 2.38–2.31 (m, 2H), 1.46–1.37 (m, 2H), 1.15–1.07 (m, 2H), 1.07–0.98 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 189.1, 169.4, 138.5, 137.4, 132.4, 129.2, 129.2, 128.8, 128.7, 128.2, 118.0, 38.7, 31.3, 30.3, 22.3, 14.1. **HRMS** (ESI) for $C_{20}H_{23}OSe$ [M+H]⁺: calculated: 359.0914, found: 359.0913; for $C_{20}H_{22}NaOSe$ [M+Na]⁺: calculated: 381.0734, found: 381.0738.

(Z)-1-phenyl-3-(phenylselanyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one
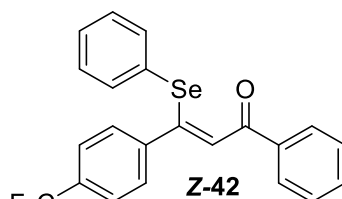
Yield for **Z-42**: 36.2 mg (84%) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.07–8.03 (m, 2H), 7.61–7.55 (m, 2H), 7.50 (t, J = 7.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.26–7.22 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H) 7.14–7.09 (m, 1H), 7.02 (t, J = 7.5 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.9, 164.0, 143.4, 138.0, 136.4, 133.0, 129.5, 129.2, 128.9, 128.7, 128.5, 128.4, 124.6 (q, J_{C-F} = 3.8 Hz), 121.1. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -62.82. **m.p.** 125 °C. **HRMS** (ESI) for $C_{22}H_{16}F_3OSe$ [M+H]⁺: calculated: 433.0318, found: 433.0319.

(Z)-1-phenyl-3-(phenylselanyl)-3-(p-tolyl)prop-2-en-1-one[16]
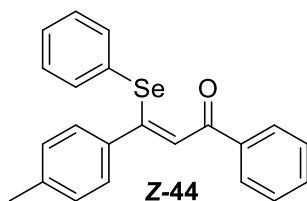
Yield for **Z-44**: 31.7 mg (84%) as a yellowish solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.05 (d, J = 8.1 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.47 (t, J = 7.7 Hz,

6. Experimental Part

2H), 7.25 (d, J = 8.0, 2H), 7.12 – 7.06 (m, 1H), 7.04 – 6.96 (m, 4H), 6.87 (d, J = 8.0 Hz, 2H), 2.21 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.9, 166.1, 138.3, 138.2, 137.1, 136.1, 136.0, 132.6, 130.5, 128.9, 128.8, 128.4, 128.3, 127.9, 120.8, 21.3. **m.p.** 106 °C. **HRMS** (ESI) for $C_{22}H_{19}OSe$ [M+H]⁺: calculated: 379.0601, found: 379.0596; for $C_{22}H_{18}NaOSe$ [M+Na]⁺: calculated: 401.0421, found: 401.0424.

(Z)-3-phenyl-3-(phenylselanyl)-1-(p-tolyl)prop-2-en-1-one
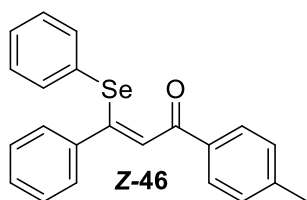
Yield for **Z-46**: 32.1 mg (85%) as a yellowish solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.96 (d, J = 7.9 Hz, 2H), 7.55 (s, 1H), 7.32–7.22 (m, 4H), 7.07 (br s, 6H), 7.00 (t, J = 7.4 Hz, 2H), 2.41 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.7, 165.3, 143.5, 139.9, 136.3, 135.7, 130.3, 129.5, 128.9, 128.5, 128.4, 128.1, 128.0, 127.6, 120.9, 21.0. **m.p.** 113 °C. **HRMS** (ESI) for $C_{22}H_{19}OSe$ [M+H]⁺: calculated: 379.0601, found: 379.0599; for $C_{22}H_{18}NaOSe$ [M+Na]⁺: calculated: 401.0421, found: 401.0422.

β-sulfonation of α,β-alkynyl ketones
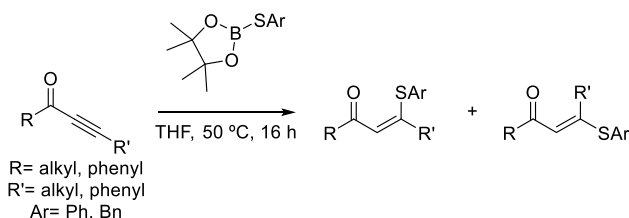
The reagents pinB-SPh (**1**) or pinB-SBn (**3**) (2 equiv.), were weighted and transferred into an oven-dried Schlenk tube inside the glovebox. The corresponding substrate (0.10 mmol) was introduced in the Schlenk tube under argon and dry THF (2 mL) was added. The mixture was stirred for 16 hours at 50 °C.

The solvent was removed under vacuum and the resulting residue was analysed by ^{1}H NMR. Conversion and selectivity were determined by ^{1}H NMR.

The product was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and ethyl acetate adequate for each case.

(Z)-4-phenyl-4-(phenylthio)but-3-en-2-one[17]
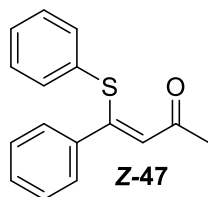
Yield for **Z-47**: 17.5 mg (69%) as a yellowish solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.16–6.99 (m, 10H), 6.49 (s, 1H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 196.4, 159.4, 138.4, 134.3, 132.6, 129.0, 128.5, 128.4, 128.0, 127.8, 123.5, 30.9. **HRMS** (ESI) for C$_{16}$H$_{15}$OS [M+H]$^+$: calculated: 255.0844, found: 255.0837; for C$_{16}$H$_{14}$NaOS [M+Na]$^+$: calculated: 277.0663, found: 277.0656.

(Z/E)-4-(phenylthio)-4-(p-tolyl)but-3-en-2-one
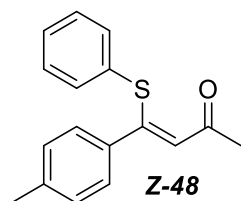
Yield for **Z-48** and **E-48**: 21.5 mg (80%) as a white solid. The stereoisomers were isolated in a ratio of 70/30 (*Z/E*).
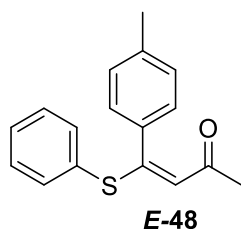
^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): δ 7.57–7.52 (m, 2H, *E*), 7.45–7.40 (m, 3H, *E*), 7.32–7.29 (m, 2H, *E*), 7.23–7.19 (m, 1H, *Z*), 7.16–7.13 (m, 2H, *Z*), 7.08–7.01 (m, *Z/E*), 6.92–6.87 (m, 2H, *Z*), 6.47 (s, 1H, *Z*), 5.66 (s, 1H, *E*), 2.38 (s, 3H, *E*), 2.34 (s, 3H, *Z*), 2.21 (s, 3H, *Z*), 2.04 (s, 1H, *E*). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 197.1, 196.5, 160.1, 159.2, 140.0, 138.6, 135.5, 135.4, 134.0, 132.9, 130.3, 130.1, 130.0, 129.4, 128.9, 128.9, 128.6, 128.5, 127.8, 123.6, 123.0, 30.9, 30.3, 21.6, 21.3. **HRMS** (ESI) for C$_{17}$H$_{17}$OS [M+H]$^+$: calculated: 269.1000, found: 269.1018; for C$_{17}$H$_{16}$NaOS [M+Na]$^+$: calculated: 291.0820, found: 291.0819.

6. Experimental Part

(Z)-4-(phenylthio)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one
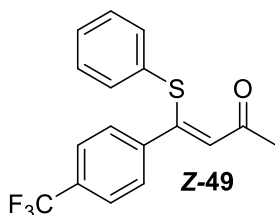
Yield for **Z-49**: 20.9 mg (65%) as a brown oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.34 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.16–7.12 (m, 2H), 7.10–7.02 (m, 3H), 6.48 (s, 1H), 2.36 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 196.3, 157.7, 141.9 (q, J_{C-F} = 1.4 Hz), 134.4, 131.1 (q, J_{C-F} = 140.7 Hz), 130.1, 129.3, 128.7, 128.5, 124.8 (q, J_{C-F} = 3.8 Hz), 123.9, 123.8 (q, J_{C-F} = 272.4 Hz), 30.9. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -62.87. **HRMS** (ESI) for $C_{17}H_{14}F_3OS$ [M+H]⁺: calculated: 323.0717, found: 323.0725.

(Z)-4-(phenylthio)non-3-en-2-one[15]
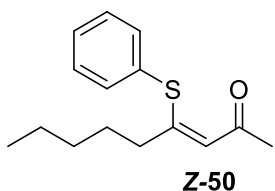
Yield for **Z-50**: 14.2 mg (57%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.56–7.51 (m, 2H), 7.43–7.33 (m, 3H), 6.30 (s, 1H), 2.25 (s, 3H), 2.14–2.01 (m, 2H), 1.37–1.28 (m, 2H), 1.14–0.95 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 196.4, 162.8, 135.9, 131.1, 129.5, 129.1, 119.4, 36.7, 31.2, 30.7, 29.5, 22.2, 14.0. **HRMS** (ESI) for $C_{15}H_{21}OS$ [M+H]⁺: calculated: 249.1313, found: 249.1314; for $C_{15}H_{20}NaOS$ [M+Na]⁺: calculated: 271.1133, found: 271.1128.

(E)-4-(phenylthio)non-3-en-2-one[18]
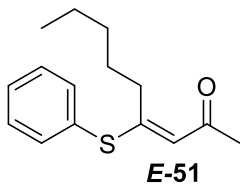
Yield for **E-50**: 7.4 mg (30%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.52–7.44 (m, 5H), 5.55 (s, 1H), 2.83–2.76 (m, 2H), 1.98 (s, 3H), 1.67–1.59 (m, 2H), 1.42–1.30 (m, 4H), 0.91 (t, *J* = 6.5 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 195.0, 166.1, 135.8, 130.1, 130.0, 129.9, 117.9, 34.0, 32.0, 31.9, 29.7, 22.7, 14.3. **HRMS** (ESI) for $C_{15}H_{21}OS$ [M+H]⁺: calculated: 249.1313, found: 249.1313; for $C_{15}H_{20}NaOS$ [M+Na]⁺: calculated: 271.1133, found: 271.1127.

138

(Z/E)-1-phenyl-3-(phenylthio)oct-2-en-1-one

Z-52

E-52
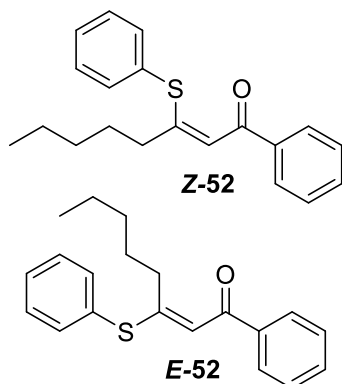
Yield for **Z-51** and **E-52**: 21.1 mg (68%) as a yellowish oil. The stereoisomers were isolated in a ratio of 49/51 (*Z/E*)

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.02–7.96 (m, 2H, *Z*), 7.62–7.33 (m, *Z/E*), 7.05 (s, 1H, *Z*), 6.28 (s, 1H, *E*), 2.94–2.89 (m, 2H, *E*), 2.28–2.22 (m, 2H, *Z*), 1.78–1.69 (m, 2H, *E*), 1.47–1.36 (m, *Z/E*), 1.16–1.02 (m, 4H, *Z*), 0.92 (t, *J* = 7.1 Hz, 3H, *E*), 0.78 (t, *J* = 7.1 Hz, 3H, *Z*). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.8 187.5, 168.0, 166.1, 139.7, 138.9, 135.9, 135.8, 132.2, 132.1, 131.4, 130.1, 130.0, 129.9, 129.5, 129.2, 128.6, 128.5, 128.2, 128.0, 115.8, 115.0, 37.4, 34.4, 32.0, 31.3, 29.8, 29.7, 22.6, 22.2, 14.2, 14.0. **HRMS** (ESI) for C₂₀H₂₂NaOS [M+Na]⁺: calculated: 333.1289, found: 333.1287.

(Z/E)-1-phenyl-3-(phenylthio)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one

Z-53

E-53
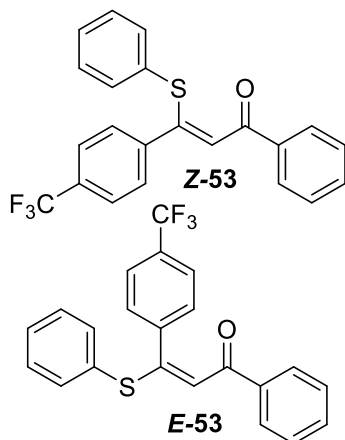
Yield for **Z-52** and **E-52**: 32.7 mg (85%) as a brown solid. The stereoisomers were isolated in a ratio of 78/22 (*Z/E*)

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.06–8.01 (m, 2H, *Z*), 7.66–7.61 (m, *Z/E*), 7.61–7.46 (m, *Z/E*), 7.44 (dt, *J* = 2.6, 1.6 Hz, 1H, *E*), 7.38 (dd, *J* = 8.7, 0.6 Hz, 2H, *Z*), 7.35 (t, *J* = 1.6 Hz, 1H, *E*), 7.33–7.28 (m, *Z/E*), 7.21 (s, 1H, *Z*), 7.20–7.17 (m, *Z/E*), 7.13–7.03 (m, *Z/E*), 6.45 (s, 1H, *E*). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.6, 188.0, 160.6, 159.5, 142.5 (q, *J*$_{C-F}$ = 1.4 Hz), 141.0 (q, *J*$_{C-F}$ = 2.6 Hz), 138.4, 138.2, 135.5, 134.5, 132.9, 132.8, 132.0, 131.1, 130.9, 130.9 (d, *J*$_{C-F}$ = 32.6 Hz), 130.8, 130.5, 130.4, 130.4 (q, *J*$_{C-F}$ = 32.6 Hz), 130.2, 130.1, 129.8, 129.4, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 125.4, 125.30 (q, *J*$_{C-F}$ = 3.8 Hz), 124.9 (q, *J*$_{C-}$

6. Experimental Part

$_F$ = 3.8 Hz), 124.1 (q, $J_{C\text{-}F}$ = 251.3 Hz), 123.8 (q, $J_{C\text{-}F}$ = 272.3 Hz), 122.7, 120.4, 120.2, 118.4. **^{19}F{^{1}H} NMR** (377 MHz, CDCl$_3$) δ (ppm): -62.73 (*E*), -62.79 (*Z*). **HRMS** (ESI) for C$_{22}$H$_{16}$F$_3$OS [M+H]$^+$: calculated: 385.0874, found: 385.0865; for C$_{22}$H$_{15}$F$_3$NaOS [M+Na]$^+$: calculated: 407.0693, found: 407.0685.

(Z)-1-phenyl-3-(phenylthio)-3-(p-tolyl)prop-2-en-1-one
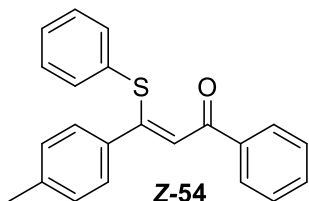
Yield for **Z-53**: 19.5 mg (59%) as a yellowish solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.06–8.02 (m, 2H), 7.57–7.52 (m, 1H), 7.51–7.45 (m, 2H), 7.22–7.18 (m, 3H), 7.13–7.03 (m, 5H), 6.96–6.91 (m, 2H), 2.23 (s, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 188.7, 162.3, 138.7, 138.6, 136.1, 134.2, 133.1, 132.5, 129.0, 128.7, 128.6, 128.5, 128.3, 127.9, 120.0, 21.3. **m.p.** 117 °C. **HRMS** (ESI) for C$_{22}$H$_{19}$OS [M+H]$^+$: calculated: 331.1157, found: 331.1173; for C$_{22}$H$_{18}$NaOS [M+Na]$^+$: calculated: 353.0976, found: 353.0977.

(Z)-3-phenyl-3-(phenylthio)-1-(p-tolyl)prop-2-en-1-one
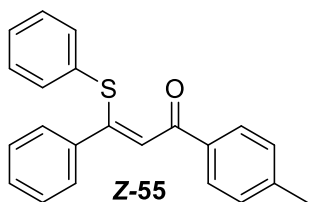
Yield for **Z-54**: 22.8 mg (69%) as a yellowish solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.96 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.22–7.18 (m, 5H), 7.15–7.11 (m, 3H), 7.08–7.04 (m, 3H), 2.42 (s, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 188.4, 161.7, 143.3, 139.0, 136.0, 134.4, 132.9, 130.0, 129.4, 129.1, 128.5, 128.4, 128.0, 127.9, 120.1, 21.8. **m.p.** 129 °C. **HRMS** (ESI) for C$_{22}$H$_{19}$OS [M+H]$^+$: calculated: 331.1157, found: 331.1175; for C$_{22}$H$_{18}$NaOS [M+Na]$^+$: calculated: 353.0976, found: 353.0979.

(Z)-4-phenyl-4-(benzylthio)but-3-en-2-one
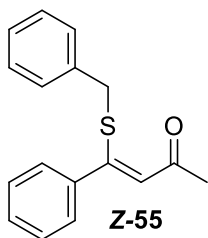
Yield for **Z-55**: 17.4 mg (65%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.40–7.37 (m, 3H), 7.28–7.23 (m, 2H), 7.20–7.14 (m, 3H), 7.01–6.95 (m, 2H), 6.31 (s, 1H), 3.61 (s, 2H), 2.24 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 196.3, 159.9, 138.6, 136.9, 129.1, 128.9, 128.6, 128.5, 128.2, 127.2, 123.8, 37.6, 30.8. **HRMS** (ESI) for C₁₇H₁₇OS [M+H]⁺: calculated: 269.1000, found: 269.0999; for C₁₇H₁₆NaOS [M+Na]⁺: calculated: 291.0820, found: 291.0816.

(Z/E)-4-(benzylthio)-4-(p-tolyl)but-3-en-2-one
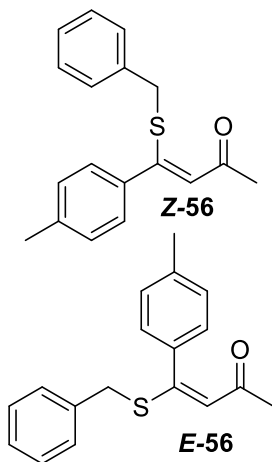
Yield for **Z-56** and **E-56**: 23.4 mg (83%) as a yellowish oil. The stereoisomers were isolated in a ratio of 72/28 (*Z/E*)

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.34–7.31 (m, *Z/E*), 7.24–7.15 (m, *Z/E*), 7.04–6.98 (m, *Z/E*), 6.30 (s, 1H, *Z*), 6.13 (s, 1H, *E*), 3.99 (s, 2H, *Z*), 3.62 (s, 2H, *E*), 2.40 (s, 3H, *Z*), 2.38 (s, 3H, *E*), 2.24 (s, 3H, *Z*), 1.79 (s, 3H, *E*). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 196.3, 160.1, 139.9, 139.1, 137.0, 135.8, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.5, 128.2, 127.8, 127.2, 123.7, 122.4, 37.9, 37.7, 30.8, 30.3, 21.5, 21.4. **HRMS** (ESI) for C₁₈H₁₉OS [M+H]⁺: calculated: 283.1157, found: 283.1156; for C₁₈H₁₈NaOS [M+Na]⁺: calculated: 305.0976, found: 305.0971.

6. Experimental Part

(Z)-4-(benzylthio)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one
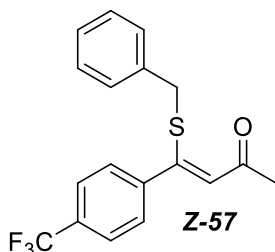
Yield for **Z-57**: 20.9 mg (62%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.62 (dd, J = 8.1, 0.5 Hz, 2H), 7.33 (dd, J = 8.0, 0.5 Hz, 2H), 7.19–7.14 (m, 3H), 6.97–6.92 (m, 2H), 6.29 (s, 1H), 3.59 (s, 2H), 2.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 196.2, 157.9, 142.1 (q, J_{C-F} = 1.6 Hz), 136.5, 130.9 (q, J_{C-F} = 32.8 Hz). 128.9, 128.6, 128.5, 127.4, 125.59 (q, J_{C-F} = 3.7 Hz), 124.4, 37.5, 30.8. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -62.70. **HRMS** (ESI) for $C_{18}H_{16}F_3OS$ [M+H]⁺: calculated: 337.0874, found: 337.0880; for $C_{18}H_{15}F_3NaOS$ [M+Na]⁺: calculated: 359.0693, found: 350.0697.

(Z)-4-(benzylthio)non-3-en-2-one
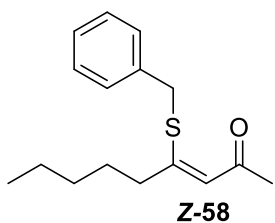
Yield for **Z-58**: 13.6 mg (52%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38–7.21 (m, 5H), 6.23 (s, 1H), 4.05 (s, 2H), 2.49–2.44 (m, 2H), 2.17 (s, 3H), 1.62–1.53 (m, 2H), 1.37–1.30 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 196.2, 162.6, 136.6, 129.2, 128.8, 127.5, 119.9, 36.7, 35.4, 31.5, 30.6, 29.8, 22.6, 14.1. **HRMS** (ESI) for $C_{16}H_{23}OS$ [M+H]⁺: calculated: 263.1470, found: 263.1467; for $C_{16}H_{23}NaOS$ [M+Na]⁺: calculated: 285.1289, found: 285.1282.

(E)-4-(benzylthio)non-3-en-2-one
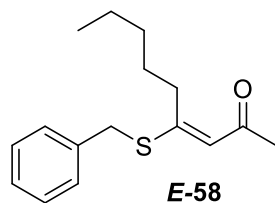
Yield for **E-58**: 10.0 mg (38%) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.39–7.26 (m, 5H), 5.94 (s, 1H), 3.99 (s, 2H), 2.80–2.70 (m, 2H), 2.14 (s, 3H), 1.61–1.51 (m, 2H), 1.39–1.27 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 194.2, 164.7, 135.0, 129.0, 128.9, 127.8, 116.2, 36.7, 34.6, 32.0, 31.9,

142

29.7, 22.5, 14.2. **HRMS** (ESI) for $C_{16}H_{23}OS$ [M+H]$^+$: calculated: 263.1470, found: 263.1467; for $C_{16}H_{23}NaOS$ [M+Na]$^+$: calculated: 285.1289, found: 285.1282.

(Z/E)-3-(benzylthio)-1-phenyloct-2-en-1-one

Z-59

E-59
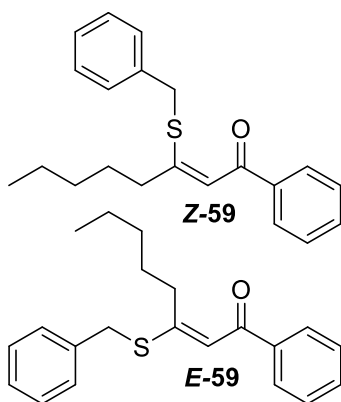
Yield for **Z-59** and **E-59**: 24.3 mg (75%) as a yellowish oil. The stereoisomers were isolated in a ratio of 84/16 (*Z/E*)

¹H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.95-7.90 (m, 2H, *Z*), 7.72–7.68 (m, 2H, *E*), 7.53–7.23 (m, *Z/E*), 6.98 (s, 1H, *Z*), 6.57 (s, 1H, *E*), 4.12 (s, 2H, *Z*), 4.11 (s, 2H, *E*), 2.80–2.83 (m, 2H, *E*), 2.65–2.59 (m, 2H, *Z*), 1.72–1.63 (m, 2.4H, *Z/E*), 1.42–1.33 (m, *Z/E*), 0.95–0.89 (m, *Z/E*). **¹³C NMR** (100 MHz, CDCl$_3$) δ (ppm): 188.5, 187.4, 166.1, 166.0, 139.9, 138.9, 136.5, 135.1, 132.1, 132.0, 129.3, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 127.6, 116.1, 113.8, 37.4, 36.8, 35.7, 35.0, 32.0, 31.5, 30.0, 29.9, 22.7, 22.6, 14.2, 14.1. **HRMS** (ESI) for $C_{21}H_{25}OS$ [M+H]$^+$: calculated: 325.1626, found: 325.1620; for $C_{21}H_{24}NaOS$ [M+Na]$^+$: calculated: 347.1446, found: 347.1439.

6. Experimental Part

(Z/E)-3-(benzylthio)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one
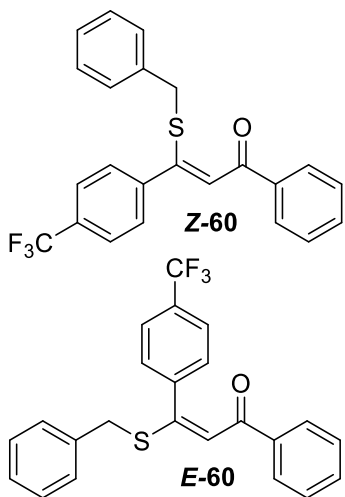
Yield for **Z-60** and **E-60**: 33.1 mg (83%) as a brown solid. The stereoisomers were isolated in a ratio of 75/25 (*Z/E*)

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.97–7.92 (m, 2H, *Z*), 7.70 (dt, *J* = 6.8, 2.3 Hz, 2H, *E*), 7.66 (d, *J* = 8.1 Hz, 2H, *Z*), 7.57 (d, *J* = 8.1 Hz, 2H, *E*), 7.55–7.35 (m, *Z/E*), 7.18–7.14 (m, *Z/E*), 7.03 (s, 1H, *Z*), 7.00–6.93 (m, *Z/E*), 6.83 (s, 1H, *E*), 4.13 (s, 2H, *E*), 3.64 (s, 2H, *Z*). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.4, 187.8, 160.9, 157.6, 142.52 (q, $J_{C\text{-}F}$ = 1.3 Hz), 141.23 (q, $J_{C\text{-}F}$ = 1.5 Hz), 138.5, 138.2, 136.4, 134.9, 132.8, 132.7, 131.1, 130.7, 131.0 (q, $J_{C\text{-}F}$ = 32.7 Hz), 130.9 (q, $J_{C\text{-}F}$ = 32.7 Hz), 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.3, 125.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.7, 122.6, 120.7, 118.1, 37.9, 37.78. **¹⁹F{¹H} NMR** (377 MHz, CDCl₃) δ (ppm): -62.66 (*Z*), -62.71 (*E*). **HRMS** (ESI) for $C_{23}H_{18}F_3OS$ [M+H]⁺: calculated: 399.1030, found: 399.1022; for $C_{23}H_{17}F_3NaOS$ [M+Na]⁺: calculated: 421.0850, found: 421.0842.

(Z)-3-(benzylthio)-1-phenyl-3-(p-tolyl)prop-2-en-1-one
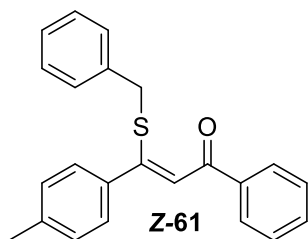
Yield for **Z-61**: 22.0 mg (64%) as a yellowish oil.
¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.97–7.93 (m, 2H), 7.53–7.48 (m, 1H), 7.46–7.40 (m, 2H), 7.27–7.15 (m, 7H), 7.07–7.02 (m, 3H), 3.68 (s, 2H), 2.42 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ (ppm): 188.5, 163.3, 139.1, 138.6, 136.9, 136.3, 132.4, 129.4, 129.2, 128.6, 128.5, 128.2, 128.2, 127.2, 119.8, 38.0, 21.5. **HRMS** (ESI) for $C_{23}H_{21}OS$ [M+H]⁺: calculated: 345.1313, found: 345.1306; for $C_{23}H_{20}NaOS$ [M+Na]⁺: calculated: 367.1133, found: 367.1131.

(Z)-3-(benzylthio)-3-phenyl-1-(p-tolyl)prop-2-en-1-one
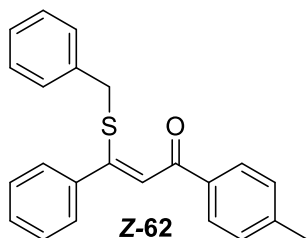
Yield for **Z-62**: 22.4 mg (65%) as a yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.86 (d, J = 8.2 Hz, 2H), 7.45–7.39 (m, 3H), 7.35–7.31 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.18–7.14 (m, 3H), 7.03 (s, 1H), 7.03–6.99 (m, 2H), 3.65 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 188.2, 162.5, 143.1, 139.2, 136.8, 136.0, 129.3, 129.1, 128.9, 128.7, 128.4, 128.4, 128.3, 127.2, 120.1, 37.8, 21.8.

HRMS (ESI) for C$_{23}$H$_{21}$OS [M+H]$^+$: calculated: 345.1313, found: 345.1326; for C$_{23}$H$_{20}$NaOS [M+Na]$^+$: calculated: 367.1133, found: 367.1130.

Synthesis of ynoates
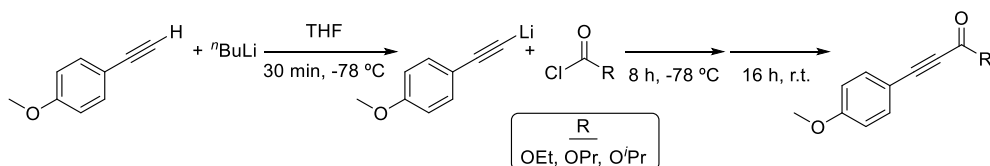
An oven-dried Schlenck equipped with a magnetic stir bar was charged with 2 mmol of the appropriate alkyne and dissolved in 3 mL of THF. At -78 ℃, 1.05 equiv. of ^{n}BuLi (1.6 M) were added dropwise. After stirring for 30 min, 1 equiv. of the alkyl chloroformate was added drop wise. After 8 h stirring the reaction was allowed to rise to room temperature and let it react overnight. The reaction was quenched with 2 mL of saturated Na$_2$S$_2$O$_4$ and extracted 3 times with 5 mL of DCM. All the organic layers were collected and dry over MgSO$_4$ and evaporated to dryness. The crude residue was analysed by ^{1}H NMR. Then the products were purified by silica gel flash chromatography.

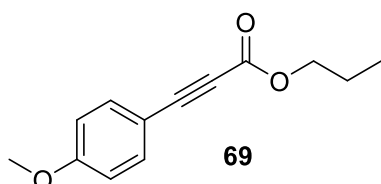6. Experimental Part

Ethyl 3-(4-methoxyphenyl)propiolate[19]
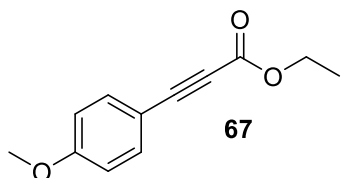
Yield for **67**: 367.6 mg (90%) as a colourless oil.

1H NMR (CDCl$_3$, 400 MHz) δ 7.53–7.49 (m, 2H), 6.87–6.84 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). **13C NMR** (CDCl$_3$, 100 MHz) δ 161.5, 154.4, 135.0, 114.3, 111.4, 86.9, 80.2, 62.0, 55.4, 14.2. **HRMS** (ESI) for C$_{12}$H$_{13}$O$_3$ [M+H]$^+$: calculated: 205.0865, found: 205.0862.

Propyl 3-(4-methoxyphenyl)propiolate

Yield for **69**: 388.5 mg (89%) as a yellowish oil.

1H NMR (CDCl$_3$, 400 MHz) δ 7.55–7.51 (m, 2H), 6.89–6.85 (m, 2H), 4.17 (t, J = 6.8 Hz, 2H), 3.82 (s, 3H), 1.77–1.68 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). **13C NMR** (CDCl$_3$, 100 MHz) δ 161.5, 154.6, 135.0, 114.3, 111.4, 87.0, 80.2, 67.6, 55.5, 22.0, 10.5. **HRMS** (ESI) for C$_{13}$H$_{15}$O$_3$ [M+H]$^+$: calculated: 219.1021, found: 219.1018.
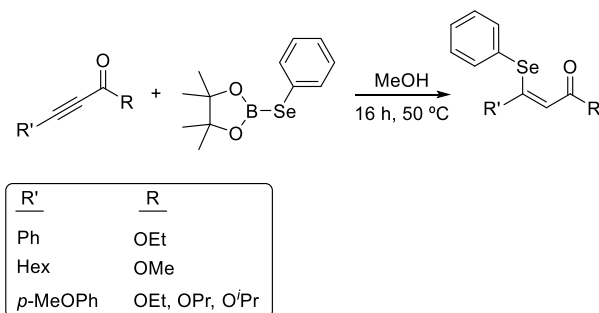
Isopropyl 3-(4-methoxyphenyl)propiolate
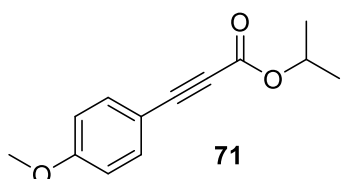
Yield for **71**: 379.8 mg (87%) as a white solid.

**1H NMR** (CDCl$_3$, 400 MHz) δ 7.56–7.52 (m, 2H), 6.89–6.86 (m, 2H), 5.15 (hept, J = 6.3 Hz, 1H), 3.83 (s, 3H), 1.33 (d, J = 6.3 Hz, 6H). **13C NMR** (CDCl$_3$, 100 MHz) δ 161.5, 154.1, 135.0, 114.4, 111.6, 86.6, 80.6, 69.9, 55.5, 21.9. **HRMS** (ESI) for C$_{13}$H$_{15}$O$_3$ [M+H]$^+$: calculated: 219.1021, found: 219.1017.

146

1,4-selenation of ynoates

R'	R
Ph	OEt
Hex	OMe
p-MeOPh	OEt, OPr, O^{i}Pr

In the glove-box, an oven-dried resealable vial equipped with a magnetic stir bar was charged with 0.2 mmol of the ynoate compound. Then, the vial was charged with 1.1 equiv. of pinB-SePh (**4**) with 0.15 mL of dry MeOH. After 16 h at 50 ºC the reaction was evaporated to dryness. The crude residue was analysed by GC-MS and ¹H NMR using naphthalene as an internal standard. Then the products were purified by silica gel flash chromatography.

Ethyl (Z)-3-phenyl-3-(phenylselanyl)acrylate
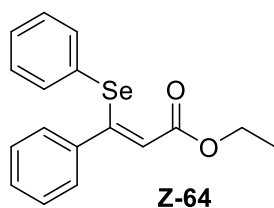
Z-64

Yield for **Z-64**: 49.0 mg (74%) as a yellowish solid.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.25–7.20 (m, 2H), 7.11–6.96 (m, 8H), 6.32 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 166.9, 161.4, 139.2, 136.4, 129.3, 128.7, 128.5, 128.1, 128.0, 127.6, 117.1, 60.7, 14.5. **HRMS** (ESI) for C$_{17}$H$_{17}$O$_2$Se [M+H]$^+$: calculated: 333.0394, found: 333.0391.

6. Experimental Part

Methyl (Z)-3-(phenylselanyl)non-2-enoate

Z-66
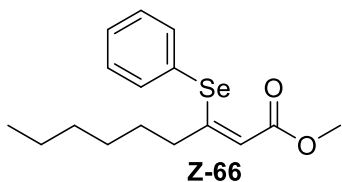
Yield for **Z-66**: 51.4 mg (79%) as a yellowish oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.69–7.65 (m, 2H), 7.43–7.38 (m, 1H), 7.36–7.32 (m, 2H), 6.16 (s, 1H), 3.76 (s, 3H), 2.17–2.13 (m, 2H), 1.34–1.26 (m, 2H), 1.17–1.10 (m, 2H), 1.05–0.97 (m, 4H), 0.79 (t, J = 7.3 Hz, 3H).**¹³C NMR** (CDCl₃, 100 MHz) δ 167.7, 164.4, 137.7, 129.3, 129.2, 127.6, 113.2, 51.5, 37.9, 31.4, 29.8, 28.5, 22.5, 14.1. **HRMS** (ESI) for $C_{16}H_{23}O_2Se$ [M+H]⁺: calculated: 327.0863, found: 327.0855.

Ethyl (Z)-3-(4-methoxyphenyl)-3-(phenylselanyl)acrylate

Z-68
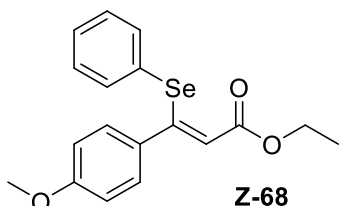
Yield for **Z-68**: 52.0 mg (78%) as a yellowish oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.24–7.21 (m, 2H), 7.11–7.07 (m, 1H), 7.04–6.95 (m, 4H), 6.58–6.54 (m, 2H), 6.30 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.68 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). **¹³C NMR** (CDCl₃, 100 MHz) δ 166.9, 161.0, 159.6, 136.1, 131.8, 130.2, 129.7, 128.5, 127.9, 116.7, 113.0, 60.6, 55.3, 14.5. **HRMS** (ESI) for $C_{18}H_{19}O_3Se$ [M+H]⁺: calculated: 363.0499, found: 363.0495.

*Propyl (Z)-3-(4-methoxyphenyl)-3-(phenylselanyl)acrylate*

Z-70
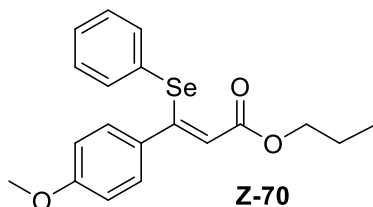
Yield for **Z-70**: 54.0 mg (72%) as a yellowish oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.24–7.22 (m, 2H), 7.11–7.07 (m, 1H), 7.03–6.95 (m, 4H), 6.57–6.54 (m, 2H), 6.31 (s, 1H), 4.19 (t, J = 6.7 Hz, 2H), 3.68 (s, 3H), 1.78–1.69 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).**¹³C NMR** (CDCl₃, 100 MHz) δ 167.0, 160.9, 159.5, 136.1, 131.7, 130.2, 129.7, 128.5, 127.8, 116.7,

148

113.0, 66.2, 55.3, 22.2, 10.6. **HRMS** (ESI) for $C_{19}H_{21}O_3Se$ [M+H]$^+$: calculated: 377.0656, found: 377.0651.

*Isopropyl (Z)-3-(4-methoxyphenyl)-3-(phenylselanyl)acrylate*
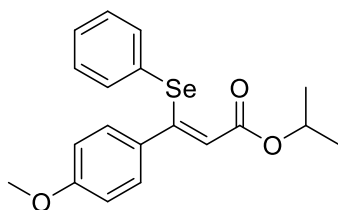
Z-72

Yield for **Z-72**: 51.8 mg (69%) as a yellowish oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.23–7.21 (m, 2H), 7.11–7.07 (m, 1H), 7.03–6.95 (m, 4H), 6.57–6.53 (m, 2H), 6.27 (s, 1H), 5.17 (hept, J = 6.2 Hz, 1H), 3.67 (s, 3H), 1.32 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 166.5, 160.6, 159.5, 136.1, 131.8, 130.2, 129.7, 128.5, 127.8, 117.2, 113.0, 67.9, 55.3, 22.2. **HRMS** (ESI) for $C_{19}H_{21}O_3Se$ [M+H]$^+$: calculated: 377.0656, found: 377.0648.

### *anti-3,4*-selenoboration of ynoates
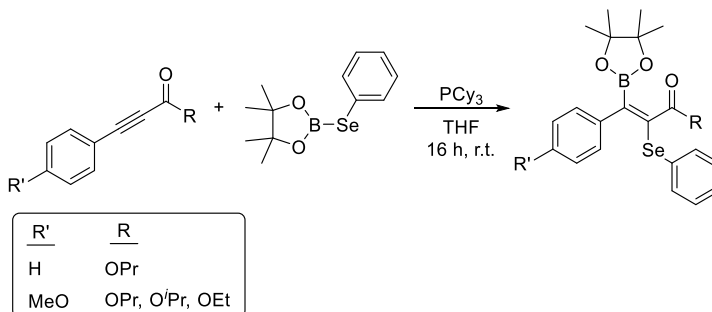
In the glove-box, an oven-dried resealable vial equipped with a magnetic stir bar was charged with 0.2 mmol of the ynoate compound. Then, 15 mol% of tricyclohexylphosphine in 0.15 ml of dry THF was added.

After stirring in the glove-box for 5 min the vial was charged with 1.1 equiv. of pinB-SePh (**4**). After 16 h at room temperature the reaction was evaporated to dryness. The crude residue was analysed by GC-MS and ^{1}H NMR using naphthalene as an internal standard. Then the products were purified by silica gel flash chromatography.

6. Experimental Part

Ethyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate

74
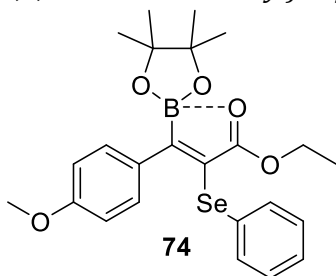
Yield for **74**: 4.9 mg (5%) as a yellowish oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.29–7.35 (m, 4H), 7.19–7.16 (m, 3H), 6.92–6.88 (m, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.29 (s, 12H), 0.94 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 169.4, 159.8, 134.5, 132.9, 131.6, 131.0, 129.9, 129.0, 127.2, 113.5, 83.9, 62.8, 55.4, 25.0, 13.7. **^{11}B NMR** (128.3 MHz, CDCl$_3$) δ 28.3. **HRMS** (ESI) for C$_{24}$H$_{30}$BO$_5$Se [M+H]$^+$: calculated: 489.1352, found: 489.1358.

Propyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate

75
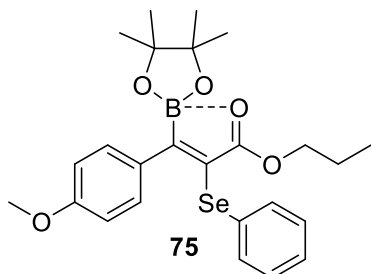
Yield for **75**: 23.1 mg, (23%) as a yellowish oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.40–7.33 (m, 4H), 7.17–7.14 (m, 3H), 6.91–6.88 (m, 2H), 3.93 (t, *J* = 6.7 Hz, 2H), 3.82 (s, 3H), 1.41–1.32 (m, 2H), 1.29 (s, 12H), 0.70 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 169.9, 159.8, 134.3, 132.3, 131.5, 131.2, 129.9, 129.0, 128.3 (bs), 127.0, 113.4, 83.8, 68.6, 55.3, 25.0, 21.6, 10.3. **^{11}B NMR** (128.3 MHz, CDCl$_3$) δ 27.9. **HRMS** (ESI) for C$_{50}$H$_{62}$B$_2$NaO$_{10}$Se$_2$ [2M+Na]$^+$: calculated: 1027.2757, found: 1027.2789.

*Isopropyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate*

76
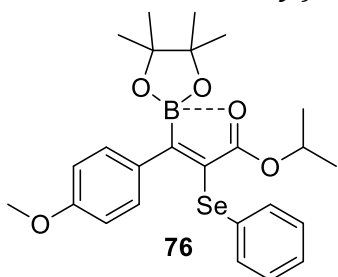
Yield for **76**: 31.1 mg (31%) as a yellowish oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.41–7.36 (m, 4H), 7.18–7.15 (m, 3H), 6.92–6.89 (m, 2H), 4.85 (hept, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 1.29 (s, 12H), 0.95 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 169.6, 159.9, 132.6, 131.5, 131.4, 130.0,

129.0, 128.3, 127.1, 113.4, 83.6, 71.3, 55.3, 25.0, 21.3. **11B NMR** (128.3 MHz, CDCl₃) δ 27.8. **HRMS** (ESI) for $C_{25}H_{31}BNaO_5Se$ [M+Na]⁺: calculated: 525.1327, found: 525.1332.

One pot α-selenation of ynoates
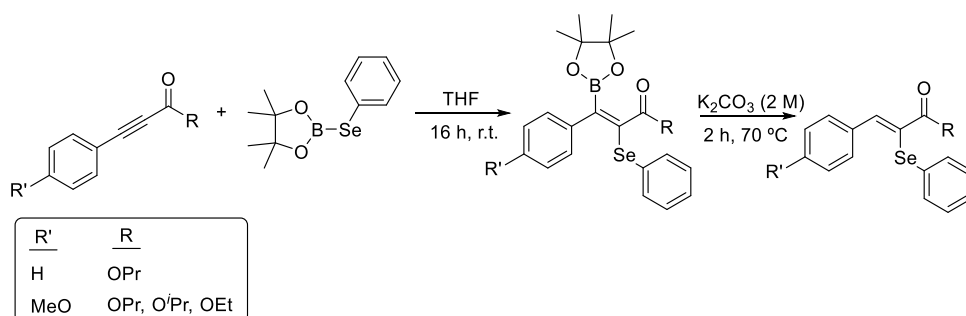
R'	R
H	OPr
MeO	OPr, OⁱPr, OEt

In the glove-box, an oven-dried resealable vial equipped with a magnetic stir bar was charged with 0.2 mmol of the ynoate compound. Then, 15 mol% of tricyclohexylphosphine in 0.15 ml of dry THF was added. After stirring in the glove-box for 5 min the vial was charged with 1.1 equiv. of pinB-SePh (**4**) . After 16 h at room temperature the reaction was evaporated to dryness. The crude residue was disolved in 2 mL of THF and 0.2 mL of K₂CO₃ (2M water solution) was added dropwise. The reaction was heated to reflux for 2 h. Then the reaction was extracted with DCM and filtered through a pad of Celite and MgSO₄. The solvent was removed and the residue was analyzed by GC-MS and ¹H NMR using naphthalene as an internal standard. Then the products were purified by silica gel flash chromatography.

Ethyl (Z)-3-phenyl-2-(phenylselanyl)acrylate
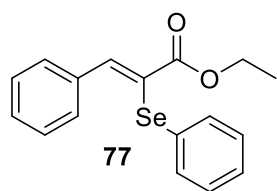
Yield for **77**: 14.6 mg (22%) as a yellowish oil.

1H NMR (CDCl₃, 400 MHz) δ 8.15 (s, 1H), 7.66–7.64 (m, 2H), 7.42–7.37 (m, 5H), 7.22–7.19 (m, 3H), 4.07 (q, J = 7.1 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H). **13C NMR** (CDCl₃, 100 MHz) δ 166.8, 145.0, 138.4, 135.3, 134.4, 131.9, 130.4,

151

6. Experimental Part

129.2, 128.3, 127.2, 124.5, 62.0, 13.9. **HRMS** (ESI) for $C_{17}H_{17}O_2Se$ [M+H]$^+$: calculated: 333.0394, found: 333.0392.
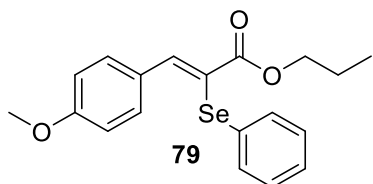
Ethyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)acrylate
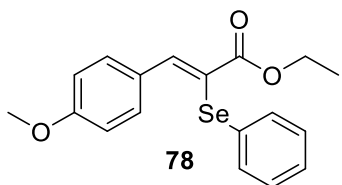
Yield for **78**: 15.2 mg (21%) as a yellowish oil.

1H NMR (CDCl$_3$, 400 MHz) δ 8.17 (s, 1H), 7.75–7.72 (m, 2H), 7.40–7.37 (m, 2H), 7.22–7.18 (m, 3H), 6.93–6.90 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). **13C NMR** (CDCl$_3$, 100 MHz) δ 167.0, 161.0, 145.8, 132.7, 131.3, 129.8, 129.2, 127.7, 127.0, 113.8, 70.7, 61.9, 55.5, 14.0. **HRMS** (ESI) for $C_{18}H_{19}O_3Se$ [M+H]$^+$: calculated: 363.0499, found: 363.0507.

Propyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)acrylate

Yield for **79**: 9.7 mg (13%) as a yellowish oil.

1H NMR (CDCl$_3$, 400 MHz) δ 8.20 (s, 1H), 7.77–7.73 (m, 2H), 7.39–7.36 (m, 2H), 7.22–7.18 (m, 3H), 6.93–6.89 (m, 2H), 4.00 (t, J = 6.7 Hz, 2H), 3.83 (s, 3H), 1.53–1.44 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H). **13C NMR** (CDCl$_3$, 100 MHz) δ 167.1, 161.0, 146.2, 136.0, 132.7, 131.0, 129.2, 127.7, 126.8, 120.4, 113.8, 67.6, 55.5, 21.9, 10.5. **HRMS** (ESI) for $C_{19}H_{21}O_3Se$ [M+H]$^+$: calculated: 377.0656, found: 377.0651.

*Isopropyl (Z)-3-(4-methoxyphenyl)-2-(phenylselanyl)acrylate*
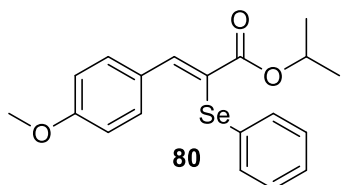
Yield for **80**: 23.3 mg (31%) as a yellowish oil.

1H NMR (CDCl$_3$, 400 MHz) δ 8.15 (s, 1H), 7.73–7.70 (m, 2H), 7.40–7.37 (m, 2H), 7.23–7.17 (m, 3H), 6.94–6.90 (m, 2H), 4.91 (hept, J = 6.2 Hz, 1H), 3.84 (s, 3H), 1.04 (d, J = 6.3 Hz, 6H). **13C NMR** (CDCl$_3$, 100 MHz) δ 166.5, 160.9, 145.3, 132.6, 131.4, 130.2, 129.2, 127.8, 126.9, 121.4, 113.8, 69.5,

55.5, 21.5. **HRMS** (ESI) for $C_{19}H_{21}O_3Se$ [M+H]$^+$: calculated: 377.0656, found: 377.0651.

6.2.4. General procedure and spectral data of Chapter 4

Insertion of pinB-SR into trimethylsilyldiazomethane
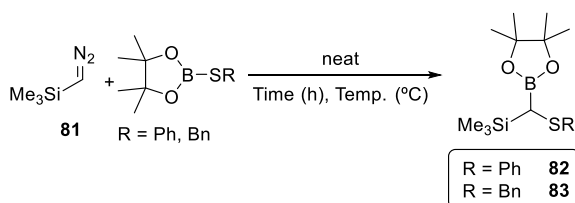
In the glove-box, an oven-dried resealable Teflon screw-cap Schlenk reaction tube equipped with a magnetic stir bar was charged with 0.5 mmol of pinB-SR (R = Ph, Bn). Then, 2 equiv. of a 2.0M solution in hexane of trimethylsilyldiazomethane (**81**) was added dropwise. After stirring in the glove-box for 5 min the Schlenk tube was sealed and heated at the corresponding temperature (pinB-SPh at 50 ºC, pinB-SBn at 70 ºC) for the appropriated time (pinB-SPh for 6h, pinB-SBn for 16h). The reaction was cooled down to room temperature, the solvent was evaporated to dryness. The crude residue was analysed by GC-MS and ^{1}H NMR. Then the products **82** and **83** were purified by silica gel flash chromatography.

Trimethyl(phenylthio)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylsilane
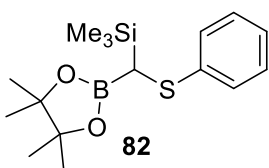

Yield for **82**: 153.1 mg (95%) as a white solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.32–7.29 (m, 2H), 7.24–7.19 (m, 2H), 7.09–7.04 (m, 1H), 2.24 (s, 1H), 1.16 (s, 6H), 1.06 (s, 6H), 0.22 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 140.2, 128.6, 126.8, 124.8, 83.9, 24.9, 24.8, -1.2.

6. Experimental Part

¹¹B NMR (128.3 MHz, CDCl$_3$) δ 33.4. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 3.0. **HRMS** (ESI) for C$_{16}$H$_{28}$BO$_2$SSi [M+H]$^+$: calculated: 323.1672, found: 323.1680.

Trimethyl(benzylthio)(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylsilane
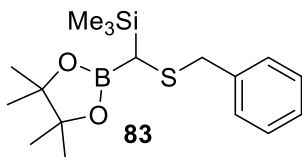
Yield for **83**: 156.4 mg (93%) as a white solid.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.32–7.27 (m, 4H), 7.25–7.17 (m, 1H), 3.78 (d, *J* = 12.9 Hz, 1H), 3.68 (d, *J* = 12.9 Hz, 1H), 1.55 (s, 1H), 1.29 (s, 12H), 0.10 (s, 9H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 138.5, 129.1, 128.5, 126.9, 83.7, 39.8, 25.5, 25.9, -1.2. **¹¹B NMR** (128.3 MHz, CDCl$_3$) δ 33.5. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 2.5. **HRMS** (ESI) for C$_{17}$H$_{30}$BO$_2$SSi [M+H]$^+$: calculated: 337,1829, found: 337,1825.

Deborylative alkylation
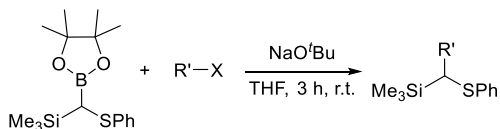
In the glove box, a 7.5 mL screw cap vial equipped with a magnetic stir bar was charged with RSCH(Bpin)(SiMe$_3$) (0.1 mmol, 1.3 equiv.) and NaO^{t}Bu (0.31 mmol, 4 equiv.). Then 0.5mL of THF was incorporated and finally the alkyl halide reagent was added (0.077 mmol, 1eq.). The reaction was stirring at room temperature for 3 h and quenched with 2 mL of saturated Na$_2$S$_2$O$_4$ and extracted 3 times with 3mL of Et$_2$O.

All the organic layers were collected and dried over MgSO$_4$ and evaporated to dryness. The crude residue was analysed by GC-MS and yields were calculated based on relative integration on the ¹H NMR compared to an internal standard (1,4-dinitrobenzene or naphthalene). Then the products were purified by silica gel flash chromatography.

154

Trimethyl-1-(phenylthio)pentadecylsilane
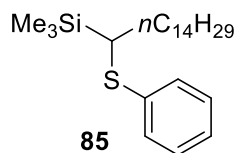
Yield for **85**: 19.6 mg (65%) as a colourless oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.38–7.33 (m, 2H), 7.29–7.23 (m, 2H), 7.17–7.12 (m, 1H), 2.47 (dd, J = 6.9, 5.2 Hz, 1H), 1.77–1.54 (m, 2H), 1.50–1.36 (m, 2H), 1.34–1.13 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 138.6, 129.4, 128.8, 125.7, 34.4, 32.1, 31.9, 29.9, 29.8 (3 x C), 29.7, 29.6, 29.5, 28.4, 22.9, 14.3, -1.9. **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 4.0. **HRMS** (APCI) C$_{24}$H$_{45}$SSi [M+H]$^+$: calculated: 393.3006, found: 393.3014.

Trimethyl-1-(phenylthio)pentylsilane
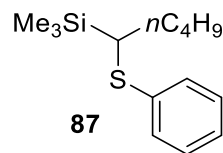
Yield for **87**: 10.8 mg (56%) as a colourless oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.37–7.33 (m, 2H), 7.28–7.23 (m, 2H), 7.17–7.11 (m, 1H), 2.47 (dd, J = 6.9, 5.2 Hz, 1H), 1.77–1.56 (m, 2H), 1.47–1.36 (m, 2H), 1.28–1.19 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 138.6, 129.4, 128.8, 125.6, 34.3, 31.5, 30.6, 22.9, 14.1, -1.9. **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 4.0. **HRMS** (EI) C$_{14}$H$_{24}$SSi [M]$^+$: calculated: 252.1368, found: 252.1368.

### 5-fluoro-1-(phenylthio)pentyltrimethylsilane
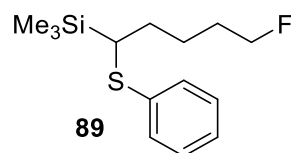
Yield for **89**: 16.8 mg (81%) as a colourless oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.37–7.33 (m, 2H), 7.28–7.23 (m, 2H), 7.18–7.13 (m, 1H), 4.42 (t, J = 5.9 Hz, 1H), 4.30 (t, J = 5.8 Hz, 1H), 2.48 (dd, J = 6.7, 5.0 Hz, 1H), 1.69–1.54 (m, 6H), 0.14 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 138.3, 129.5, 128.9, 125.9, 84.0 (d, J = 164.3 Hz), 34.4, 31.5, 30.5 (d, J = 19.5 Hz), 24.0 (d, J = 5.3 Hz), -2.0. **^{19}F{1H} NMR** (377 MHz, CDCl$_3$) δ -217.2 (m). **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 4.1. **HRMS** (APCI) C$_{14}$H$_{24}$FSSi [M+H]$^+$: calculated: 271.1347, found: 271.1348.

6. Experimental Part

5-chloro-1-(phenylthio)pentyltrimethylsilane

91
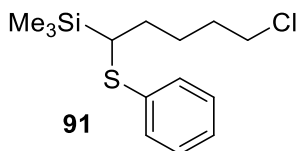
Yield for **91**: 15.7 mg (71%) as a colourless oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.37–7.34 (m, 2H), 7.29–7.24 (m, 2H), 7.18–7.14 (m, 1H), 3.45 (t, J = 6.6 Hz, 2H), 2.48 (dd, J = 6.3, 5.0 Hz, 1H), 1.75–1.56 (m, 6H), 0.15 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz) δ 138.2, 129.6, 128.9, 125.9, 44.9, 34.4, 32.7, 31.1, 25.5, -2.0. **²⁹Si NMR** (CDCl₃, 80 MHz) δ 4.1. **HRMS** (APCI) $C_{14}H_{24}ClSSi$ [M+H]⁺: calculated: 287.1045, found: 287.1051.

Trimethyl-4-phenyl-1-(phenylthio)but-3-en-1-ylsilane

93
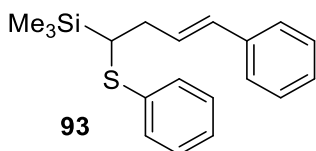
Yield for **93**: 17.8 mg (74%) as a colourless oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.40–7.36 (m, 2H), 7.29–7.21 (m, 6H), 7.20–7.12 (m, 2H), 6.36 (d, J = 15.7 Hz, 1H), 6.23 (dt, J = 15.8, 6.7 Hz, 1H), 2.69–2.61 (m, 2H), 2.58–2.50 (m, 1H), 0.16 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz) δ 137.7, 137.6, 131.2, 129.9, 129.2, 128.9, 128.5, 127.1, 126.1, 126.0, 35.4, 34.4, -1.8. **²⁹Si NMR** (CDCl₃, 80 MHz) δ 4.6. **HRMS** (APCI) $C_{19}H_{25}SSi$ [M+H]⁺: calculated: 313.1441, found: 313.1440.

Trimethyl3-methyl-1-(phenylthio)but-3-en-1-ylsilane

95
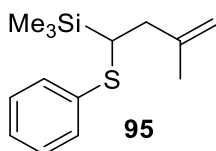
Yield for **95**: 13.7 mg (78%) as a colourless oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.39–7.34 (m, 2H), 7.29–7.22 (m, 2H), 7.18–7.13 (m, 1H), 4.81–4.74 (m, 2H), 2.65 (t, J = 7.4 Hz, 1H), 2.43 (dd, J = 14.6, 7.0 Hz, 1H), 2.33 (dd, J = 14.7, 7.6 Hz, 1H), 1.63 (s, 3H), 0.13 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz) δ 144.2, 137.9, 130.1, 128.8, 126.0, 112.7, 40.5, 31.9, 22.2, -2.0. **²⁹Si NMR** (CDCl₃, 80 MHz) δ 5.1. **HRMS** (APCI) $C_{14}H_{23}SSi$ [M+H]⁺: calculated: 251.1278, found: 251.1276.

Trimethyl-2-phenyl-1-(phenylthio)ethylsilane
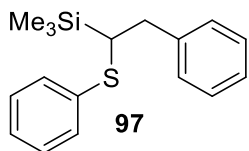
Yield for **97**: 16.5 mg (75%) as a colourless oil.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.24–7.07 (m, 10H), 3.01 (dd, J = 14.2, 7.0 Hz, 1H), 2.92 (dd, J = 14.1, 7.6 Hz, 1H), 2.74 (t, J = 7.3 Hz, 1H), 0.06 (s, 9H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 140.9, 137.7, 130.0, 129.34, 128.8, 128.3, 126.3, 126.0, 38.2, 36.8, -2.1. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 4.6. **HRMS** (APCI) C$_{17}$H$_{23}$SSi [M+H]$^+$: calculated: 287.1284, found: 287.1279.

Trimethyl-1-(phenylthio)hex-3-yn-1-ylsilane
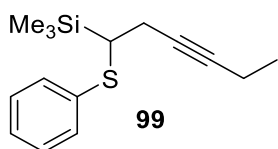
Yield for **99**: 12.3 mg (61%) as a colourless oil.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.40–7.37 (m, 2H), 7.31–7.25 (m, 2H), 7.20–7.14 (m, 1H), 2.61 (dd, J = 7.2, 4.9 Hz, 1H), 2.54–2.49 (m, 2H), 2.13 (m, 2H), 1.08 (t, J = 7.5 Hz, 3H), 0.21 (s, 9H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 137.1, 129.7, 129.0, 126.1, 83.5, 78.3, 33.0, 21.7, 14.1, 12.6, -1.8. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 5.2. **HRMS** (APCI) C$_{15}$H$_{23}$SSi [M+H]$^+$: calculated: 263.1284, found: 263.1284.

Trimethyl-1-(phenylthio)undec-10-en-1-ylsilane
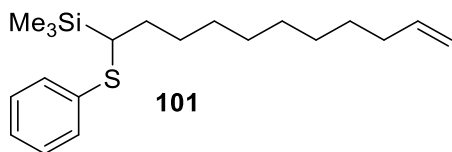
Yield for **101**: 17.3 mg (67%) as a colourless oil.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.37–7.33 (m, 2H), 7.29–7.23 (m, 2H), 7.17–7.12 (m, 1H), 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ddd, J = 17.1, 3.6, 1.6 Hz, 1H), 4.93 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 2.47 (dd, J = 6.9, 5.2 Hz, 1H), 2.05–1.99 (m, 2H), 1.76–1.56 (m, 2H), 1.45–1.14 (m, 12H), 0.13 (s, 9H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 139.4, 138.6, 129.5, 128.9, 125.7, 114.3, 34.5, 34.0, 31.9, 29.9, 29.6 (2 x C), 29.3, 29.1, 28.5, -1.9. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 4.0. **HRMS** (APCI) C$_{20}$H$_{35}$SSi [M+H]$^+$: calculated: 335.2223, found: 335.2224.

6. Experimental Part
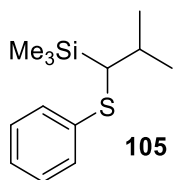
Trimethyl-2-methyl-1-(phenylthio)propylsilane

Yield for **105**: 12.5 mg (68%) as a colourless oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.39–7.34 (m, 2H), 7.28–7.22 (m, 2H), 7.16–7.10 (m, 1H), 2.52 (d, J = 2.9 Hz, 1H), 2.17 (heptd, J = 6.8, 3.0 Hz, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 139.9, 129.1, 128.8, 125.5, 42.9, 31.4, 22.3, 21.1, -0.7. **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 5.2. **HRMS** (APCI) C$_{13}$H$_{23}$SSi [M+H]$^+$: calculated: 239.1284, found: 239.1276.

(2,2-Diphenyl-1-(phenylthio)ethyl)trimethylsilane
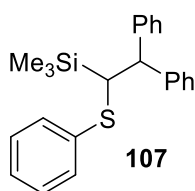
Yield for **107**: 4.2 mg (15%) as a colourless oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.36–7.27 (m, 5H), 7.22–7.12 (m, 5H), 7.07–7.04 (m, 3H), 6.97–6.94 (m, 2H), 4.27 (d, J = 9.2 Hz, 1H), 3.16 (d, J = 9.2 Hz, 1H), -0.09 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 144.0, 143.2, 138.9, 130.5, 129.1, 128.6, 128.48, 128.1, 126.6, 126.4, 125.9, 54.9, 42.9, -1.3. **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 3.9. **HRMS** (EI) for C$_{23}$H$_{26}$SSi [M]$^+$: calculated: 362.1525, found: 362.1532.

Deborylative alkylation applied to substrate 83
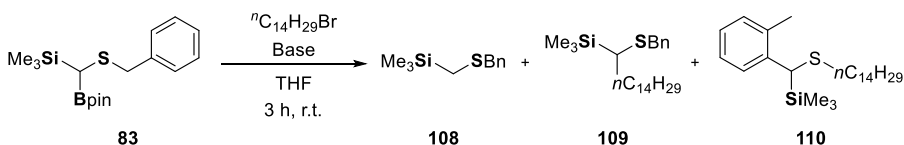
An oven-dried resealable Teflon screw-cap Schlenk reaction tube equipped with a magnetic stir bar was charged under Argon with **83** (0.1 mmol, 1 equiv.) and NaO^{t}Bu (4 equiv.). Then 0.5 mL of THF was incorporated and finally the 1-bromotetradecane was added (1 equiv.). The reaction was stirring at room temperature for 3h and quenched with 2mL of saturated Na$_2$S$_2$O$_4$ and extracted (3x) with 3mL of Et$_2$O. All the organic layers were collected and dry over MgSO$_4$ and evaporated to dryness.

The crude residue was analysed by GC-MS and yields were calculated based on relative integration on the ^{1}H NMR compared to an internal standard (1,4-dinitrobenzene).

(Benzylthio)methyltrimethylsilane[20]

108
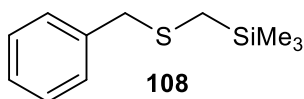
Yield for **108**: 12.6 mg (60%) as a colourless oil. **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.34–7.28 (m, 4H), 7.26–7.21 (m, 1H), 3.69 (s, 2H), 1.66 (s, 2H), 0.05 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 138.6, 129.1, 128.1, 126.9, 40.5, 17.9, -1.5.

Trimethyl(tetradecylthio)(o-tolyl)methylsilane

110
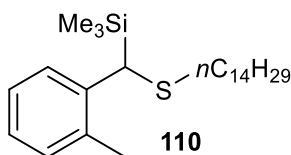
Yield for **110**: 4.5 mg (11%) as a colourless oil. **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.54 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 6.3 Hz, 1H), 7.02 (dd, J = 7.2, 1.3 Hz, 1H), 3.57 (s, 1H), 2.33–2.17 (m, 5H), 1.71–1.13 (m, 24H), 0.88 (t, J = 6.9 Hz, 3H), 0.04 (s, 9H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 140.5, 134.9, 129.9, 128.0, 126.3, 124.9, 33.6, 32.5, 32.0, 29.8, 29.8, 29.81, 29.7, 29.7, 29.6, 29.5, 29.5, 29.2, 28.9, 22.8, 20.5, 14.3, -2.3. **^{29}Si NMR** (CDCl$_3$, 80 MHz) δ 4.0. **HRMS** (EI) for C$_{25}$H$_{46}$SSi [M]$^+$: calculated: 406.3090, found: 406.3085.

Selective protodesilylation
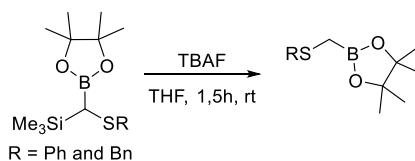

An oven-dried resealable Teflon screw-cap Schlenk reaction tube equipped with a magnetic stir bar was charged under Argon with substrates **82** or **83** (0.1 mmol, 1 equiv.).

6. Experimental Part

Then 0.5 mL of THF was incorporated and 4 equiv. (0.4 mmol) of a 1 M solution of TBAF in THF were added dropwise at 25 °C. The reaction was then stirring for 1.5 h at this temperature, quenched with saturated $Na_2S_2O_4$ and passed over a silica gel plug. The crude residue was analysed by GC-MS and yields of species C were calculated based on relative integration on the ^{1}H NMR compared to an internal standard (naphthalene). Then the product was purified by silica gel flash chromatography.

2-((Benzylthio)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

111

Yield for **111**: 17.7 mg (67%) as a colourless oil.

^{1}H NMR (CDCl₃, 400 MHz) δ 7.30 (m, 4H), 7.31–7.19 (m, 1H), 3.71 (s, 2H), 1.84 (s, 2H), 1.26 (s, 12H). **^{13}C NMR** (CDCl₃, 100 MHz) δ 138.3, 129.1, 128.5, 126.9, 84.0, 38.7, 24.9. **^{11}B NMR** (128.3 MHz, CDCl₃) δ 32.2. **HRMS** (ESI) for $C_{14}H_{21}BNaO_2S$ [M+Na]⁺: calculated: 287.1253, found: 287.1246.
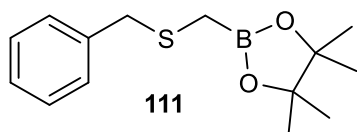
4,4,5,5-tetramethyl-2-((phenylthio)methyl)-1,3,2-dioxaborolane

112
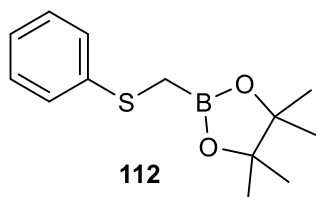
Yield for **112**: 16.5 mg (66%) as a colourless oil.

^{1}H NMR (CDCl₃, 400 MHz) δ 7.29–7.22 (m, 4H), 7.12–7.08 (m, 1H), 2.41 (s, 2H), 1.22 (s, 12H). **^{13}C NMR** (CDCl₃, 100 MHz) δ 138.8, 128.8, 127.1, 125.2, 84.4, 24.8. **^{11}B NMR** (128.3 MHz, CDCl₃) δ 32.1. **HRMS** (APCI) for $C_{13}H_{20}BO_2S$ [M+H]⁺: calculated: 251.1277, found: 251.1285.

Deprotonation/alkylation
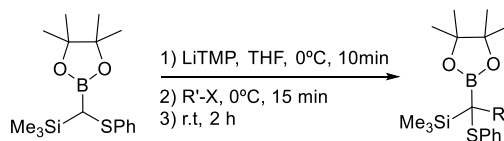
1) LiTMP, THF, 0ºC, 10min
2) R'-X, 0ºC, 15 min
3) r.t, 2 h

In the glove box, an oven-dried resealable Teflon screw-cap Schlenk reaction tube equipped with a magnetic stir bar was charged with LTMP (0.21 mmol, 1.05 equiv.) and 0.8 mL of dried THF. The flask was sealed, removed from the glove box and the reaction mixture was cooled to 0 ºC. Under Argon a solution of substrate **82** (0.2 mmol, 1 equiv.) in THF (0.2 mL) was added via syringe and the mixture was allowed to stir at 0 °C for 10 minutes. The corresponding electrophile (0.24 mmol, 1.2 equiv.) was added dropwise and the reaction was allowed to stir at 0 ºC for 15 min. Upon completion, the reaction mixture was warmed to room temperature, filtered through a silica gel plug, rinsed with diethyl ether and dichloromethane, and concentrated in vacuo. The crude reaction mixture was purified on silica gel.
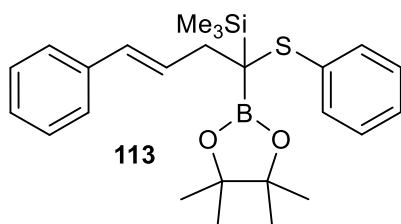
(E)-trimethyl(4-phenyl-1-(phenylthio)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)silane

Yield for **113**: 61.4 mg (70%) as a colourless oil.

¹H NMR (CDCl₃, 400 MHz) δ 7.58–7.53 (m, 2H), 7.31–7.25 (m, 4H), 7.22–7.16 (m, 4H), 6.33 (dd, *J* = 10.3, 9.2 Hz, 1H), 6.52 (ddd, *J* = 15.9, 7.1, 6.2 Hz, 1H), 2.43 (d, *J* = 16.0 Hz, 1H), 2.75 (dd, *J* = 15.3, 7.1 Hz, 1H), 1.19 (s, 6H), 1.17 (s, 6H), 0.20 (s, 9H). **¹³C NMR** (CDCl₃, 100 MHz) 138.0, 136.0, 133.8, 130.8, 130.2, 128.5, 128.3, 127.0, 126.8, 126.1, 83.8, 37.2, 25.5, 24.9, -1.5. **¹¹B NMR** (128.3 MHz, CDCl₃) δ 33.9. **²⁹Si NMR** (CDCl₃, 80 MHz) δ 6.1. **HRMS** (ESI) for C₂₅H₃₅BNaO₂SSi [M+Na]⁺: calculated: 438.2334, found: 438.2336.

6. Experimental Part

Trimethyl(2-phenyl-1-(phenylthio)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)silane
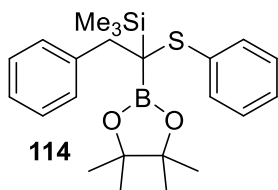
Yield for **114**: 34.6 mg (42%) as a colourless oil.

¹H NMR (CDCl$_3$, 400 MHz) δ 7.53–7.49 (m, 3H), 7.22–7.12 (m, 2H), 7.02–6.93 (m, 3H), 6.87–6.80 (m, 2H), 3.38 (d, *J* = 13.6 Hz, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 1.18 (s, 6H), 1.09 (s, 6H), 0.16 (s, 9H). **¹³C NMR** (CDCl$_3$, 100 MHz) δ 141.1, 137.3, 131.2, 131.1, 127.8, 127.8, 126.3, 125.6, 83.9, 38.8, 25.4, 25.1, -1.9. **¹¹B NMR** (128.3 MHz, CDCl$_3$) δ 32.8. **²⁹Si NMR** (CDCl$_3$, 80 MHz) δ 6.2. **HRMS** (ESI) for C$_{23}$H$_{33}$BNaO$_2$SSi [M+Na]$^+$: calculated: 435.1961, found: 435.1957.

162

6.3. References

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

2   S. A. Westcott, J. D. Webb, D. I. McIsaac, C. M. Vogels, WO Pat., 2006/089402 A1, **2006**.

3   G. Perin, E. L. Borges, T. J. Peglow, E. J. Lenardão, *Tetrahedron Lett.* **2014**, *55,* 5652–5655

4   D. Lanari, R. Ballini, S. Bonollo, A. Palmieri, F. Pizzo, L. Vaccaro, *Green Chem.* **2011**, *13*, 3181-3186.

5   T. C. Wabnitz, J. B. Spencer, *Org. Lett.* **2003**, *5*, 2141–2144.

6   Y. -Z. Li, Y. Wang, G. -F. Du, H. -Y. Zhang, H. -L. Yang, L. He, *Asian J. Org. Chem.* **2015**, *4,* 327-332.

7   A. Peng, R. Rosenblatt, K. Nolin, *Tetrahedron Lett.* **2012**, *53*, 2712–2714.

8   J. Liua, X. Xiea, S. Ma, *Synthesis* **2012**; *44*, 1569-1576.

9   P. Wessig, G. Müller, R. Herre, A. Kühn, *Helv. Chim. Acta* **2006**, *89*, 2694-2719.

10   M. Georgy, P. Lesot, J.-M. Campagne, *J. Org. Chem.* **2007**, *72*, 3543–3549.

11   J. A. Morales-Serna, A. Sauza, G. Padrón de Jesús, R. Gaviño, G. García de la Mora, J. Cárdenas, *Tetrahedron Lett.* **2013**, *54*, 7111-7114.

12   S. Atobe, H. Masuno, M. Sonoda, Y. Suzuki, H. Shinohara, S. Shibata, A. Ogawa, *Tetrahedron Lett.* **2012**, *53*, 1764-1767.

13   Y. Jeong, B.-I. Kim, J. K. Lee, J.-S. Ryu *J. Org. Chem.* **2014**, *79*, 6444-6455.

14   B. Battistelli, T. Lorenzo, M. Tiecco, C. Santi, *Eur. J. Org. Chem.* **2011**, *10*, 1848-1851.

15   G. Perin, S. R. Mendes, M. S. Silva, E. J. Lenardão, R. G. Jacob, P. C. dos Santos, *Synthetic. Commun.* **2006**, *36*, 2587-2595.

16   X.-L. Zheng, X.-L. Xu, Y.-M. Zhang, *Chinese J. Chem.* **2004**, *22*, 958-965.

Chapter 6

6. Experimental Part

17 M. S. Inkpen, A. J. P. White, T. Albrecht, N. J. Long, *Chem. Commun.* **2013**, *49*, 5663-5665.

18 E. J. Lenardão, M. S. Silva, S. R. Mendes, F. de Azambuja, R. G. Jacob, P. C. S. dos Santos, G. Perin, *J. Braz. Chem. Soc.* **2007**, *18*, 943-950.

19 P. R. Andrew, R. I. Brinkworth, A. C. partridge, J. A. Reiss, *Aust. J. Chem.* **1988**, *41*, 1717-1725.

20 D. J. Ager, *J. Chem. Soc., Perkin Trans. 1* **1986**, 195-204.

"Molta gent petita, en molts llocs petits,

*fent coses petites, pot canviar el món"*

**Eduardo Galeano**

Chapter 7

Summary

Molecules containing B-S or B-Se bonds are of great value in synthetic chemistry due to the presence of a strong Lewis acid component next to a soft Lewis base. A novel family of B-Y species (Y = S, Se) (Figure 7.1) were developed and patented in 2006 by Wescott's group but its reactivity was not further explored.[1]

pinB-SePh   pinB-SPh   pinB-STol   pinB-SBn
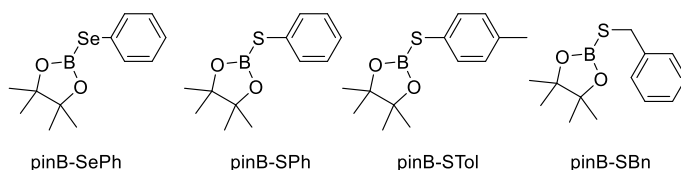
Figure 7.1. Chalcogenoboranes synthetized in Wescott's group.

In this line, we found interesting to take advantage of the "*pull-push*" effect of the B in the B-Y reagents (Y = S and Se), to selective add the sulfur or selenium moieties to unsaturated substrates to generate a new methodology towards the synthesis of organosulfides and organoselenides.

Based on previous work in the group we became determined to demonstrate the activation of pinB-SPh, pinB-STol and pinB-SBn by α,β-unsaturated ketones and aldehydes and provide an alternative sulfa Michael addition, that does not need catalysts or drastic reactions conditions to generate a new C_β-S bond (Scheme 7.1).


R= Ph, Tol and Bn; R'= R"= Ar, Alkyl
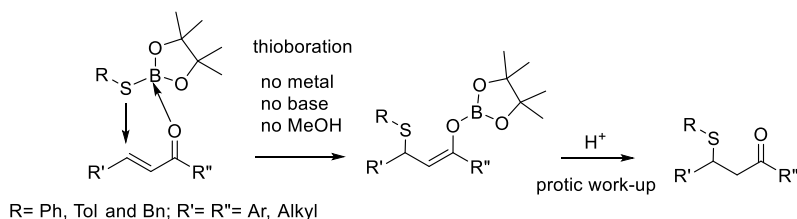
Scheme 7.1. Expected reactivity of the vinyl carbonyl compounds with B-S reagents.

The thioboration generates 1,4-addition as well as 1,2-addition intermediates, depending on the structural nature of the substrate.

Protic workup delivers the corresponding β-sulfido carbonyl compounds in good isolated yields (up to 81% I.Y.). A family of 15 β-sulfido carbonyl compounds have been synthetized through the direct thioboration/protonation, where the PhS, TolS, and BnS moieties have been delivered from the thiodioxaborolanes pinB-SPh, pinB-STol and pinB-SBn by the simple activation of the Bpin moiety with a carbonyl group.

Through the powerful "*pull-push*" properties of Bpin units in the chalcogenoborate reagents pinB-SePh, pinB-SPh and pinB-SBn we also explored the reactivity with ynones, in a metal free context without any additive except MeOH as solvent. We were able to report a total of 26 examples of synthesis of vinyl selenides and vinyl sulfides up to 84% isolated yield and with high regioselectivity towards the *Z*-isomer (Scheme 7.2). The mechanistic proposal allows to justify and to understand the selectivity of the reaction outcome.
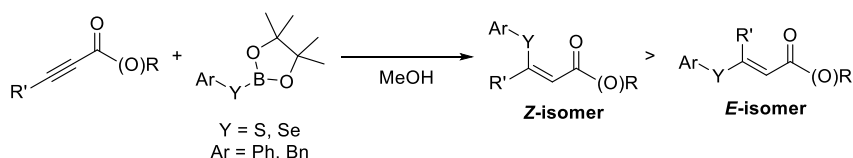
Scheme 7.2. Synthesis of vinyl chalcogenides throughout chalcogenoborates.

When the reaction is carried out with ynoates and pinB-SePh the C-Se bond is also generated in the β-position generating 5 *Z*-vinyl selenides conjugated to esters in moderated isolated yields (up to 79% I.Y.). When the reaction is carried out in the presence of tricyclohexyl phosphine the formation of an *anti*-3,4-selenoborated products takes place. Four examples with moderated NMR yields has been reported and further functionalized through protodeboronation to afford the corresponding α-phenylselenated compounds has also been explored (Scheme 7.3).
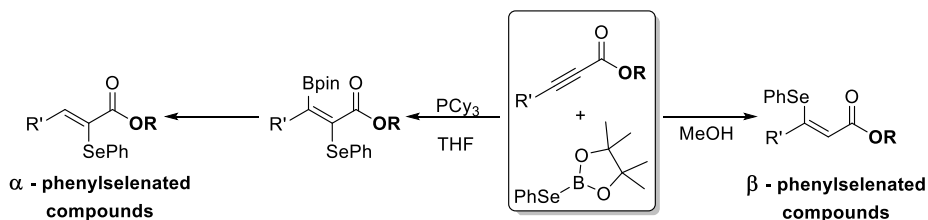
Scheme 7.3. β-Selenation vs. *3,4-anti*-selenoboration of α,β-acetylenic esters.

Having in mind that the insertion of diazo compounds into a σ-bond[2] represents one of the most efficient approaches to form new C-X bonds (X = N, O, S, Si, etc.)[3] and the previous work done in our group in the insertion of diazo compounds into the unsymmetrical B-B bond of pinB-Bdan,[4] the last project of this thesis consists in the insertion of $(CH_3)_3SiCHN_2$ into pinB-SPh and pinB-SBn reagents. We plan this reaction with the objective of afford and easy and direct synthesis of main group, multisubstituted sp^3 carbons (Si, B, S). The further functionalization of this $HC(SR)(Bpin)(SiMe_3)$ could help to increase structurally diverse molecules of synthetic potential (Scheme 7.4).
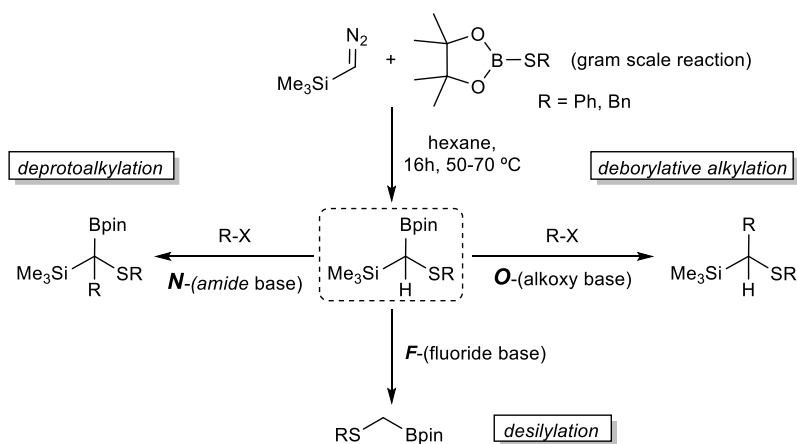


Scheme 7.4. Strategic (trimethylsilyl)diazomethane insertion into pinB-SR, followed by selective functionalizations.

169

The (trimethylsilyl)diazomethane insertion into the B-S σ-bond of pinB-SPh and pinB-SBn afforded HC(SR)(Bpin)(SiMe$_3$) in quantitative yields when was carried out in a gram scale.

A wide scope of 12 alkyl halides can be used for the selective functionalization of the Bpin moiety through deborylative alkylation with sodium *tert*-butoxide when reacted with HC(SPh)(Bpin)(SiMe$_3$). The alkylated products were obtained up to 81% isolated yield. When this reaction is performed with HC(SBn)(Bpin)(SiMe$_3$) a rearranged product is observed and its formation can be explained through a Sommelet-Haüser rearrangement (Scheme 7.5).
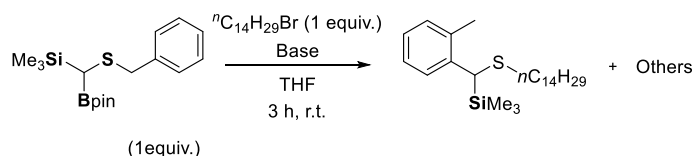
Scheme 7.5. Deborylative alkylation of HC(SBn)(Bpin)(SiMe$_3$) affording the rearranged product through a Sommelet-Haüser process.

By using TBAF is possible to desilylate the inserted products obtaining the thioborated product in moderated isolated yields. By using LTMP with the inserted products is possible to abstract the proton and alkylate the α-boron and α-silyl stabilized carbanion with alkyl halides to afford highly functionalized products.

170

References

1   S. A. Westcott, J. D. Webb, D. I. McIsaac, C. M. Vogels, WO2006/089402 A1, **2006**.

2   T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.

3   a) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918-4931; b) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377.

4   A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó, E. Fernández, *Org. Biomol. Chem.* **2015**, *13*, 9659-9664.

Chapter 7

172

Appendix

Publications

"Strategic trimethylsilyldiazomethane insertion into pinB-SR followed by selective alkylations."

Authors: M. G. Civit, J. Royes, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernàndez.

Journal: *Org. Lett.* **2016**, *18*, 3830-3833.

"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***,357,* 3098-3103.

"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,* 2148-2154.

"Organocatalytic functionalisation through boron chemistry"

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

Journal: *Pure Applied Chemistry **2015**, 87,*181-194.

Appendix

Conference contributions

EUROBORON 7   04/09/2016 – 08/09/2016

Suzdal, Russia

Young Oral Presentation: *"Modular synthesis of main-group (Si, B, S) multisubstituted carbons and subsequent alkylation assisted by Bpin moieties."*

Authors: M. G. Civit, J. Royes, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernàndez.

Summer School 2016

on Molecular Boron Chemistry   25/07/2016 – 29/07/2016

Würzburg, Germany

Poster: *"Strategic trimethylsilyldiazomethane insertion into pinB-SR, followed by selective alkylation methods."*

Authors: M. G. Civit, J. Royes, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernández.

XXVI Reunión Bienal

de Química Orgánica   14/06/2016 – 17/06/2016

Punta Umbría, Spain

Poster: *"Modular synthesis of main-group (Si, B, S) multisubstituted carbons and subsequent alkylation assisted by Bpin moieties."*

Authors: M. G. Civit, J. Royes, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernández.

Poster: *"Straightforward alkylation of H-C(SR)(Bpin)(SiMe$_3$) with alkylhalides: untouchable borons."*

Authors: J. Royes, M. G. Civit, C. M. Vogels, S. A. Westcott, A. B. Cuenca, E. Fernández.

176

ISySyCat 2015   02/09/2015 – 04/09/2015

Evora, Portugal

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

Chemical Science Poster Prize

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

OMCOS 18   26/06/2015 – 02/07/2015

Sitges, Spain

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

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

XV IMEBORON   24/08/2014 – 28/08/2014

Prague, Czech Republic

Poster and Flash Presentation: *"Enones activate ArS-Bpin to synthesize 4-sulphanyl ketones."*

Authors: <u>M. G. Civit</u>, C. M. Vogels, S. A. Westcott, E. Fernández.

XXXII Congreso GEQO   17/09/2014 – 19/09/2014

Tarragona, Spain

Poster: *"Enones activate ArS-Bpin to synthesize 4-sulphanyl ketones."*

Authors: <u>M. G. Civit</u>, C. M. Vogels, S. A. Westcott, E. Fernández.

178

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

UNIVERSITAT ROVIRA I VIRGILI
AVANCES EN SISTEMAS INTERACTIVOS PARA PERSONAS CON PARÁLISIS CEREBRAL
Marc Garcia Civit

UNIVERSITAT
ROVIRA i VIRGILI