α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.

Gerard Palau Lluch

Dipòsit Legal: T 1358-2015

UNIVERSITAT ROVIRA I VIRGILI

GERARD PALAU LLUCH

Ph.D Thesis

2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION

Ph.D Thesis

Gerard Palau Lluch

Departament de Química Física i Inorgànica

Supervised by Dr. Mª Elena Fernández

2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

Gerard Palau Lluch

α,β-Difunctionalization of α,β-unsaturated carbonyl compounds through borylation reaction

---

Ph.D Thesis

Supervised by

Dr. Mª Elena Fernández

Departament de Química Física I Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona

2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

UNIVERSITAT ROVIRA I VIRGILI
DEPARTAMENT DE QUÍMICA FÍSICA I INORGÀNICA
Campus Sescelades
Marcel·lí Domingo, s/n
43007 Tarragona
Tel. +34 977 55 81 37
Fax +34 977 55 95 63
www.quimica.urv.es

FAIG CONSTAR que aquest treball titulat "α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION" que presenta en Gerard Palau Lluch per a l'obtenció de títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Física i Inorgànica d'aquesta universitat i que compleix els requeriments per poder optar a Menció Europea.

Tarragona, 5 de Juny de 2015

Dr. Maria Elena Fernández

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

UNIVERSITAT ROVIRA I VIRGILI
α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

El present treball ha estat desenvolupat amb una beca FPI finançada per el Ministerio de Ciencia e Innovación. Els següents projectes han finançat el treball que descriu la següent tesis:

Referència ajuda: BES-2011-045568.

Referència projecte: CTQ2010-16226.

Títol del projecte: DESARROLLO DE LA QUÍMICA CATALÍTICA ORGANOBORADA SELECTIVA MEDIANTE METALES DE TRANSICIÓN ECONOMICAMENTE VIABLES.

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

UNIVERSITAT ROVIRA I VIRGILI
α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL
COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

Acknowledgements

Doncs bé, ha arribat el moment, aquell moment que tots temem i a la vegada esperem amb tanta il·lusió, el moment en que gairebé quatre anys de "vida" es resumeixen en un únic llibre. No voldria per això començar sense dedicar unes paraules a tots aquells que han aportat el seu gra de sorra per a fer que aquesta tesi esdevingui una realitat.

Primer de tot, i sense cap mena de dubte, vull agraïr a la meva supervisora Dr. Elena Fernández, per donar-me la oportunitat de realitzar la tesi sota la seva tutela, però també vull aprofitar per dir-te que gràcies a tu he pogut també viure el que encara ara han sigut les experències més boniques i enriquidores de la meva vida, com han sigut la meva estància Erasmus durant la carrera i després aquell any que vaig treballar a la Universitat de Potsdam a Alemanya, i com no aquells mesos a la Universitat de Oxford. Tot això m'ha fet crèixer com a persona i tu n'ets la primera a qui en puc donar les gràcies. Gràcies també Elena per incansables tardes per intentar resoldre dubtes químics, per la teva gentilesa i les paraules d'ànim, i sobretot per saber compaginar tant bé èpoques de molta feina i grans exigències, amb moments de lleure amb els membres del grup (dinars, sopars, sortides varies, etc), en l'equilibri de tot rau l'autèntic sentit de les coses, i tu li has sabut donar sempre.

També vull agraïr a la resta de professors del grup de heterogènia i homogènia per ajudar-me sempre que ho he necessitat, durant el màster i després també durant el doctorat.

Voldria també agraïr al Ministerio de Ciencia e Innovación per la beca FPI la qual he sigut destinatari.

I would like to thank Prof. Veronique Gouverneur for giving me the opportunity to stay for three months in her Research Group in Oxford during my Doctoral studies. It has been a fantastic experience. Working in one of the most cutting-edge centers concerning research and innovation is something I will never forget. Of course a big thank you to all the members of the group for the wonderful atmosphere and for your help during my stay, and specially those afternoons we spent at the pub eating fish and chips and drinking a couple pints. Special mention to Jessica, Oscar, Begoña, Enrico, Faye, Jamie, Tanatorn, Lukas, Miriam, Stefan, you guys are awesome!

Actually in this almost four years and before that, many people have crossed paths with me in my life, and I will try to somehow mention them all in this small text.

First of all, for my Erasmus in Tübingen and my stay in Potsdam, this goes to all my German friends which I still keep contact with:

Die Freunde, die ich in Tübingen und Potsdam kennengelernt habe, waren der Anfang von allem. In Deutschland habe ich bemerkt, dass ich ein Forscher werden möchte. Dort hab ich ein sehr schönes Land entdeckt und auch die einige der interessantesten Leute, die ich bis jetzt kennen gelernt habe. Ihr seid einfach die besten. Ich möchte euch für die wunderbaren gemeinsamen Momente danken und dank euch kann ich auch ein einigermaßen „verständlisches“ Deutsch sprechen. Und noch das wichtigste... Die Deutsche können mich noch verstehen! Danke an meine Mitbewohner in Tübingen - Johannes, Linda und Andrea. Danke auch Jessica und Daniel, danke Jenni, Helena, Silvio, Emmanuel... Die kleinen Ausflüge, die wir ab und zu am Wochenende mit dem Fahrrad gemacht haben waren immer total cool. Danke meinem Mitarbeiter in Potsdam - Dr. Piotr Cywinski, Prof. Hans-Gerd Löhmannsröben, Sascha, Sören, Claudia, Uschi, Lydia (es ist schon lange her und es kann sein, dass ich noch viele, viele Leute zu erwähnen vergessen habe, aber ihr alle seid in meiner Erinnerung). Ihr seid ein wichtiger Teil meiner Thesis.

Auch möchte ich Barbara danken, meiner Tandempartnerin hier in Tarragona und auch eine sehr gute Freundin von mir. Du hast mir geholfen, dass mein Deutsch noch gut klingt! Wirklich vielen Dank! Zu guter Letzt möchte ich auch noch Jacqueline erwähnen. Danke, dass du ab und zu mit geredet hast. Das hat mir auch geholfen mein Deutsch zu bewahren und auch wenn wir uns noch nicht richtig kennen, glaube ich in dir ein sehr hübsches und nettes Mädel kennen gelernt zu haben.

This goes for my italian friends, which I met around the globe under different circumstances:

Adesso che ho scritto in tedesco, anche dovrei scrivere qualche parola in Italiano, per tutti gli italiani e italiane che ho conosciuto in questi anni e che anche mi hanno fatto imparare una bellissima lingua e mi hanno fatto conoscere une delle Terre piu belle che esistono, la Italia. Grazie Vittoria, Chiara, Paula, Maria Andrea, Alba, Thomas, Roberto, Francesco, Gianluca e tanti altri che adesso sicuramente anche dimentico, un pezzo di questa tesi e anche vostra.

Anche grazie a te Enrico! Sei il migliore e piu divertente! Ho riduto tantissimo con te nel laboratorio, ti ringrazio per i momenti vissuti quel’anno che sei stato nella cappa vicina alla mia, spero ci vediamo presto! Fra un’anno sei dottore anche te! Dai forza ce la fai!

Tornem al català, perquè on puc fer els agraïments més amplis en quan a la tesi es refereix, és amb la gent que he conviscut dia a dia durant aquests gairebé 4 anys. Aquí ve una de les parts més difícils de la tesi... Espero no deixar-me res ni ningú!

Primer de tot als meus companys de grup, els que ja no hi són com la Cristina Solé, la Cristina Pubill, l'Amadeu, la Jessica, gràcies pel vostre suport des del minut zero i quan era un estudiant de màster que en prou feines sabia que era un schlenck. Obviament també gràcies a tu Xavi! Ets molt crack tiu, gràcies per les converses, les ajudes informàtiques, els dinars compartits, i la bona música que tant tu com jo escoltem. També als nous, la Núria i el Marc, compartir espai, vivències i material amb vosaltres ha sigut tot un plaer. Continueu amb la bona feina i amb la mateixa il.lusió que teniu ara. Ana para ti también unas palabras, gracias por tu buen humor y por tu immensa sabiduria química la cual siempre estas dispuesta a compartir con nosotros.

Per els doctorands, amics, i companys de feina i de „aventures", MOLTÍSSIMES GRÀCIES!! Anar d'un en un faria de aquests agraïments quelcom interminable, i en algun moment m'hauré de posar a escriure la tesi, no? Només dir-vos que he après moltíssim al costat vostre, coses bones casi sempre (tot i que hi ha hagut moments de tota manera), però d'això es tracta la convivència i la vida en general. Quan passin els anys i recordi aquest periode tant important de la meva vida que he viscut aquí, jo em quedaré sens dubte amb les coses bones que tots vosaltres de una manera o altra m'heu ofert. A tots vosaltres, Alberto, Marc Magre, Jèssica Margalef, Laia, Elisabet, als qui ja no hi són Jessica Llop, Javi, Mercè, Itziar, Angy i als més nous però que alguns ja porteu un any llarg aquí com a doctorands i altres que heu acabat de començar el màster, Laura, Fàtima, Toni, Aaron, Fran, Carlota, Nannette. Us queda encara un llarg camí per recòrrer (a altres un camí no tant llarg) però la satisfacció quan s'acava és infinita, continueu lluitant pels vostres somnis.

Tampoc vull deixar d'agraïr a bons amics i companys també del pis de dalt i de l'edifici de davant, Jordi Colavida, Stefano, Jorge, Isma, Joan Guasch, Xavier Montané, Emma i tots els demés! Gràcies per la simpatia i com no gràcies pel „contraband" de productes i material que hem fet de un pis a l'altre, amb companyerisme així dóna gust treballar!

Voldria també agraïr a aquelles persones que fora de les parets de la Universitat han estat allí per algún que altre sopar, padel, cine, calçotada, estona a la platja, festes, concerts, etcètera. Aquestes paraules són per vosaltres Adri, Angy, Ramón, Coll, Roser, Elisabet, Sisco, Judith, Sandra. I altres que de tant en tant també us veig però potser no tant sovint, moltes gràcies!

UNIVERSITAT ROVIRA I VIRGILI
α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL
COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

Finalment, agraïr a les persones més importants que tinc ara mateix, als meus pares i la meva germana. Aquesta tesi si que és seva, tot el suport, totes les alegries i les tristors se les han endut ells, i tot i ser el seu deure com a familia no era ni molt menys la seva obligació fer-ho, els hi estaré eternament agraït i els hi retornaré el favor tantes vegades com em sigui possible.

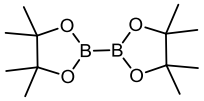
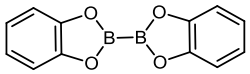
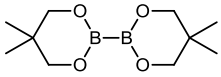
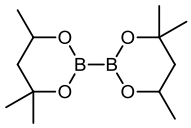
Table of contents

Abbreviations

Solvents

CD_3Cl	-	Deuterated chloroform
DCM	-	Dichloromethane
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
DME	-	Dimethoxyethane
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
THF	-	Tetrahydrofuran
Py	-	Pyridine
DCE	-	Dichloroethane

Reagents

B_2pin_2	-	
B_2cat_2	-	
B_2neop_2	-	
B_2hex_2	-	

Others

A	-	Armstrong(s)
Hz	-	Herz
J	-	Coupling constant (NMR)

M.S.	-	Molecular sieves
MS	-	Mass Spectrometry
GC	-	Gas Chromatography
HRMS	-	High Resolution Mass Espectrometry
ESI TOF	-	Electrospray Ionization Time-of-flight
M	-	Molar, 1M = 1 mol/dm^3
mol	-	Mole(s)
ppm	-	parts per milion
ee	-	enantiomeric excess
Bn	-	Benzyl
Ph	-	Phenyl
iPr	-	iso-Propyl
tBu	-	tert-Butyl
NHC	-	N-heterocyclic carbene
IBX	-	2-iodobenzoic acid
PCC	-	Pyridinium chlorochromate
BAIB	-	(Diacetoxyiodo)benzene

The important thing is not to stop questioning,

Curiosity has its own reason for existing. One cannot

Help but to be in awe about when he contemplates the mysteries

Of eternity, of life, of the marvelous structure of reality.

It is enough of one tries merely to comprehend

A little of this mystery every day.

Never lose a holy curiosity.

(Albert Einstein)

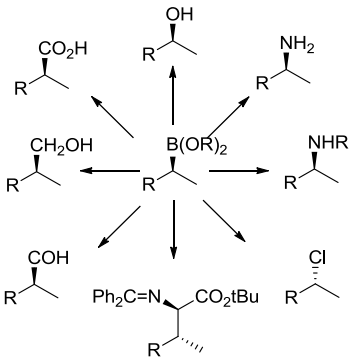
1. INTRODUCTION. CATALYTIC β-BORATION REACTION. RECENT APPROACHES.

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

1. Introduction on boron chemistry

Organoboranes are of great interest in both synthetic chemistry and biomedical sciences[1,2]. The main advantages of using organoboranes as intermediates in organic synthesis are their versatile reactivity, stability and easy accessibility[1]. In particular, the catalytic C-B bond formation can be considered as an ideal way to introduce functionalities and obtain target products with high control of chemo-, regio-, and stereoselectivity (Scheme 1.1).



Scheme 1.1. *Specific transformations of the C-B bond.*

During the 20th century, chemists revealed a vast array of reactions involving boron reagents which demonstrated their utility in organic synthesis. Most notable was the 1979 Nobel Prize in Chemistry, awarded to H. C. Brown and Georg Wittig for their development of the use of boron and phosphorus-containing compounds, respectively, into important reagents in organic chemistry[3]. In particular, H. C. Brown was pioneer in hydroboration reaction[4].

The hydroboration methodology became of particular interest to synthetic chemists as it allowed the regioselective addition of boron containing species to the least substituted carbon in olefinic species. The subsequent transformation of carbon boron bonds into C-C[5,6], C-N[7,8], C-O and C-X bonds and homologations[9] resulted of great value. Other transformations have been widely explored in the literature[10-13] and subsequently, organoboron reagents have become key reagents in organic synthesis[14-16]. More recently, Akira Suzuki was also awarded, along with Richard F. Heck and Ei-ichi Negishi with the 2010 Nobel prize in chemistry for the contribution to develop palladium-catalyzed cross-coupling methodology (Suzuki-Miyaura cross-coupling), using organoboron compounds.

1.1 Catalytic β-boration reaction

Within the last decades, chemists have developed a process which is commonly known as β-boration (or boron conjugate addition, BCA) of activated olefins[17,18]. This is a process by which diboron species [e.g. B_2pin_2 (pin = $OCMe_2CMe_2O$) **1**, B_2cat_2 (cat = 1,2-$O_2C_6H_4$) **2**, B_2neop_2 (neop = $OCH_2CMe_2CH_2O$) **3**, B_2hex_2 (hex = $OC(Me)_2CH_2CH(Me)O$) **4** (Figure 1.1) undergo Michael-type conjugate addition to an electron-deficient alkene **5**, leading to a 1,4-addition adduct **6** which after work-up, yields the β-borated product through hydrolysis or methanolisis (Scheme 1.2).

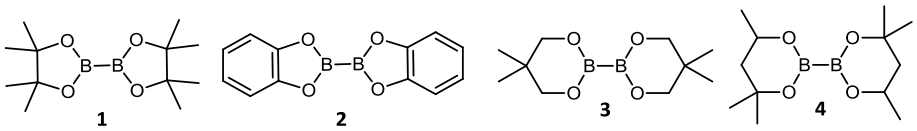
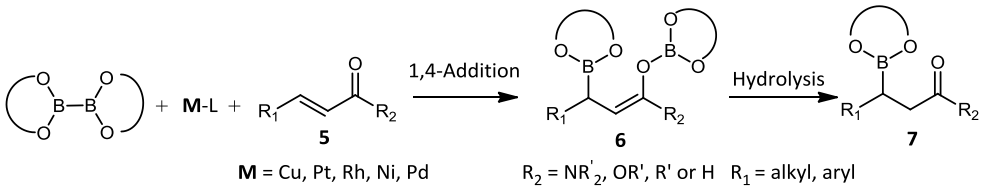
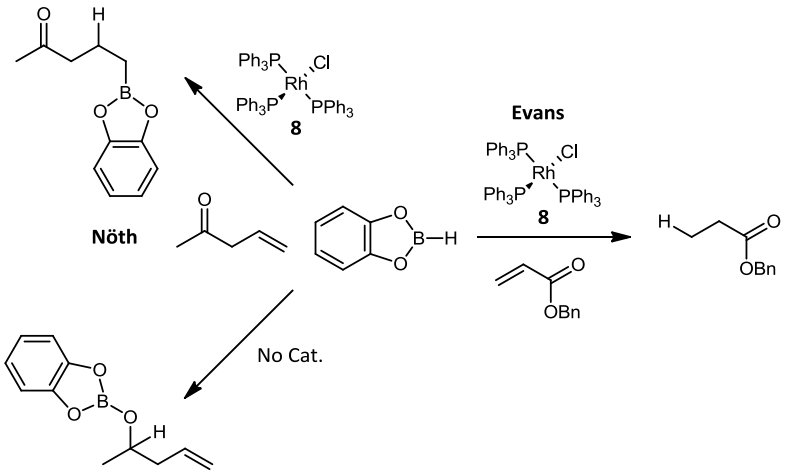


Figure 1.1. *Diboron species B_2pin_2 **1**, B_2cat_2 **2**, B_2neop_2 **3** and $B_2(hex)_2$ **4**.*

The first example of this process was reported in 1997 by Marder et al[19]. At that time, metal-catalyzed diboration of simple alkenes was becoming well-explored and, in this context, the diboration of conjugated electron-deficient alkenes seemed an attractive prospect[20]. Indeed, Nöth et al. had demonstrated the hydroboration of simple alkenes using Wilkinson's catalyst ($RhCl(PPh_3)_3$) (**8**) in the presence of other functional groups[21]. Later, Evans and coworkers revealed an elegant conjugate reduction methodology using Wilkinson's catalyst **8** in conjunction with catecholborane (H-Bcat)[22](Scheme 1.3), introducing the hydride in the β-position.

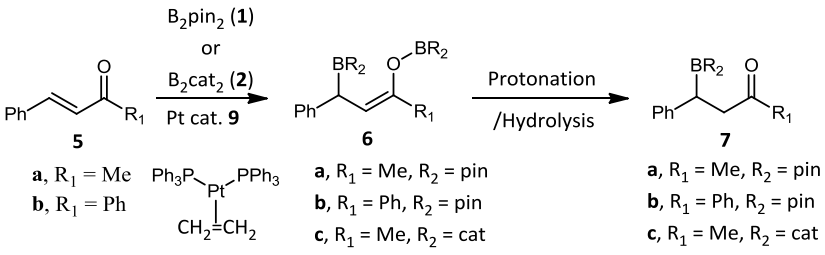


Scheme 1.2. *Metal-catalyzed β-boration (via 1,4-diboration).*



Scheme 1.3. *Evan's conjugate reduction and the Nöth hydroboration methodology.*

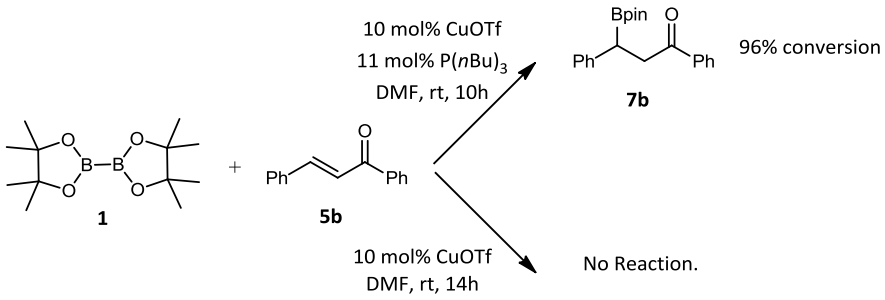
Studies involving the metal-catalyzed diboration of unsaturated species were becoming increasingly explored[23-24] towards difunctionalization through cross-coupling reactions[25]. In response to the need for novel routes to organoboron reagents, Marder and coworkers demonstrated the diboration of two α,β-unsaturated ketones (**5a** and **5b**) with B_2pin_2 (**1**) and B_2cat_2 (**2**) in the presence of platinum catalysts $[Pt(C_2H_4)(PPh_3)_2]$ (**9**) (Scheme 1.4). The addition of water on the diborated intermediate **6a-c** resulted in the β-borated products **7** in stoichiometric conversions. It is interesting to note that there are only two examples in the literature were 1,4-diborated products of electron-deficient alkenes have been isolated and characterized, likely due to their moisture sensitivity. However, isolation of the 1,4-diboron species **6a**, **6b** and **6c** provided valuable mechanistic insights[19,26].



Scheme 1.4. *Diboration followed by aqueous work-up yields β-borated products **7a-c**.*

Those first reports in 1997[19] and 2004[26] also provided a new pathway to β-hydroxy ketones (aldol products) via the oxidation of boron functionalities. Marder et al. also noted that reactions between α,β-unsaturated ketones and chiral diboron reagents were potentially interesting, hinting at the potential of β-boration to be enantioselective. However, the first attempts did not provide any success.

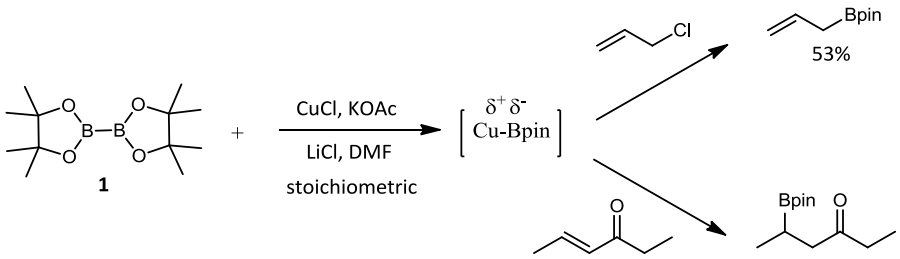
In 2000, Hosomi and coworkers[27] unveiled the first example of a copper-catalyzed β-boration on a series of α,β-unsaturated ketones, closely followed by Miyaura and his team[28,29]. The former report was analogous to their previous work involving the use of disilane reagents, using copper catalysis to transfer silyl groups into the β-position of electron deficient alkenes[30]. Hosomi's group probed the utility of the copper-catalyzed system in the β-boration of chalcone **5b** and B_2pin_2 (**1**). Initial attempts failed; however, further attempts showed that the addition of P(*n*Bu)$_3$ followed by hydrolysis gave the desired β-boration product **7b** (Scheme 1.5). Hosomi et al. then probed the optimized reaction of this β-boration methodology using a series of enones, both cyclic and acyclic, resulting in conversions ranging from 67-96%. The reaction proceeded with only the addition of a phosphine ligand alone, albeit in low yield (7%). The role of the phosphines in the β-boration reactions will be discussed later.



Scheme 1.5. *Hosomi's Cu-catalyzed β-boration protocol for α,β-unsaturated species.*

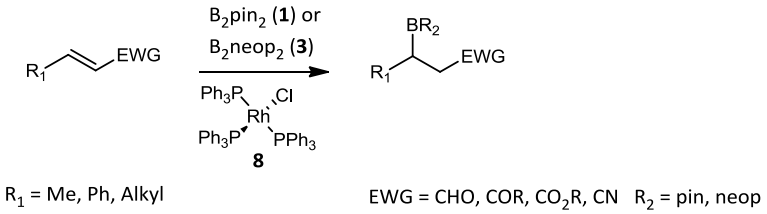
Miyaura et al. further demonstrated the utility of a copper catalyzed system[28-29] using stoichiometric amounts of CuCl, LiCl, KOAc in DMF in the β-boration of a series α,β-unsaturated esters, ketones and nitriles. Interestingly, Miyaura was the first to suggest and provide evidence for a boryl copper species as providing the nucleophilic source of boron in the β-boration reaction[28]. They provided evidence for this by introducing allyl chloride into their copper-boryl system, the result of which gave an allyl boronate species (Scheme 1.6). This

result is consistent with the assumed presence of a copper-boron species acting as a nucleophilic source of boron[17,31](Scheme 1.6).



Scheme 1.6. *Evidence for the nucleophilic Cu-Bpin species presented by Miyaura.*

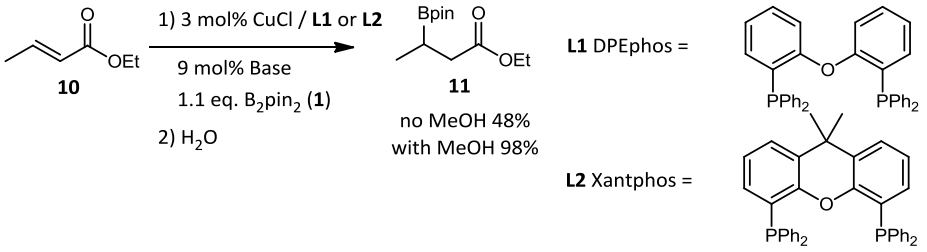
In addition to the already mentioned work of Hosomi and Miyaura, Kabalka et al. demonstrated the use of Wilkinson's catalyst in the β-boration of electron-deficient alkenes[32], consisting on α,β-unsaturated ketones, esters, and nitriles (Scheme 1.7) as an approach to boronic acids for application in boron neutron capture therapy[33]. They probed the use of Wilkinson's catalyst **8** to catalyze the β-boration reaction of activated olefins. This work adjusted some problems associated with the high catalyst loadings previously reported by Miyaura[28,29]. Typically only 10 mol% of Wilkinson's catalyst **8** was required compared to the stoichiometric copper catalyst loadings in the Miyaura's β-boration protocol



Scheme 1.7.*Wilkinson's catalyst for the β-boration of electron-deficient alkenes*

Later on, Yun and coworkers[34] , revolutionized the area by revealing a novel methodology which enabled the β-boration of α,β-unsaturated esters, ketones and nitriles. This methodology was achieved using a copper-based reaction system, modified with phosphines. Yun et al. had previously developed an efficient protocol for the conjugate reduction of α,β-unsaturated nitriles[35] using copper catalysis and xanthene-type biphosphine ligands, which were key to improve the activity and lower catalyst loadings. When applied to the β-boration reaction, Yun et al. showed that xanthene-type biphosphine ligands improved the nucleophilicity of the active copper hydride species, which resulted in an improved

methodology for the chemoselective conjugate reduction of α,β-unsaturated nitriles[35]. Previous evidence[28] suggested that the active copper species in β-boration was a nucleophilic copper-boryl species and therefore Yun et al. examined whether the observed increase in nucleophilicity (as observed in the active copper-hydride case) could be applied to the active copper-boryl species in the β-boration of α,β-unsaturated species. They first attempted the β-boration of (E)-ethyl crotonate **10** using copper (I) salt, ligand and a slight excess of B_2pin_2 (**1**) at room temperature for 14h (Scheme 1.8). Their initial attempt used a copper(I) acetate salt and DPEphos **L1** in the absence of base. GC analysis showed a 26% conversion to **11**, which then compared to previous literature examples was poor[27,28,32]. However, by changing to copper(I) chloride with the addition of sodium *tert*-butoxide (9 mol%) the reaction improved and the yield of the β-boration product doubled to 48%. Changing the ligand from DPEPhos to Xantphos **L2** resulted in poor conversion to the β-borated product. Yun et al. noted in their previous work on the conjugate reduction of α,β-unsaturated nitriles[35] that the addition of alcohol to their reaction improved yields dramatically.



Scheme 1.8. *Yun's methodology for β-boration of α,β-unsaturated esters.*

Buchwald et al. had shown that the addition of ethanol could protonate an organocopper intermediate and improve reaction yields due to improved catalytic turnover, where the suggested mechanistic pathway proceeded via a carbon-bound copper intermediate[36].

With this idea in hand, Yun et al. used an alcohol additive in their reaction by means of protonation of the assumed carbon-bound copper intermediate. Indeed, they found that the addition of *tert*-butanol or methanol dramatically improved yields in their reactions. The use of copper(I) chloride (3 mol%), DPEphos **L1** (3 mol%), sodium *tert*-butoxide (9 mol%) and methanol (2.2 eq.), gave the β-boration products in up to 98% yield[34].

The dramatic influence of the addition of the alcohol was clear and extended to related substrates (Table 1.1) giving higher yields compared to that obtained by Hosomi et al. and

using a lower catalyst loading (3 mol%). Not only was the addition of an alcohol in the copper catalyzed β-boration of electron-deficient alkenes shown to be an important step forward, Yun et al. also demonstrated that this protocol was potentially interesting for the enantioselective perspective[34].

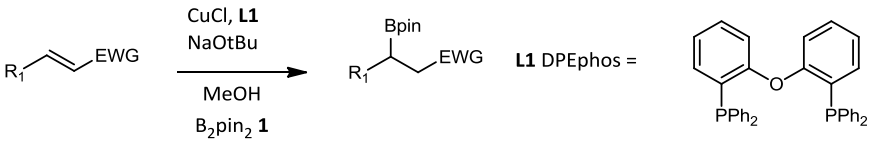
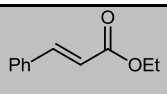
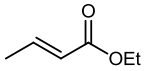
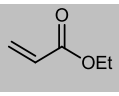
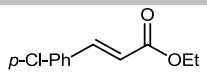
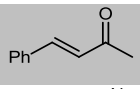
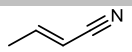


Table 1.1. *Influence of methanol on the β-boration of electron deficient alkenes.*

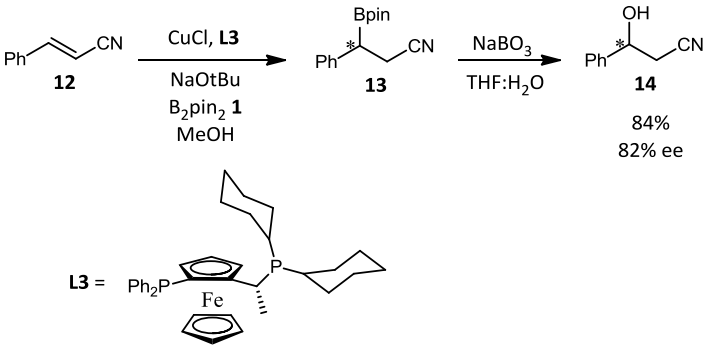
Entry	Species	Time (h)	Yield [a,b]
1		11	91
2		14.5	95
3		1.5	98
4		16	93
5		14	95
6		6.5	95

*[a]Reaction conditions = CuCl (3 mol%), **L1** (3 mol%), NaOtBu (9 mol%), B_2pin_2 (**1**) (1.1 eq.), MeOH (2.2 eq.), THF.*
[b]Isolated Yield.

1.2 Asymmetric metal-catalyzed β-boration.

During the early development of the β-boration methodology, it was suggested that this process had the potential to be enantioselective, perhaps by employing chiral diborane reagents, as suggested by Marder et al[19]. Interestingly, Yun et al. developed an enantioselective β-boration protocol, not based upon chiral diborane reagents, but on a catalytic system that employed chiral phosphine ligands[34,37,38]. Having shown that the copper catalyzed β-boration of cinnamonitrile **12** gave the borated product **13** in high yield (95%), Yun et al. applied the chiral Josiphos ligand **L3** to their optimized methodology. This was followed by C-B oxidation to yield the chiral β-hydroxy nitrile **14** with the expected complete

retention of stereochemistry. Product **14** was obtained in a 84% yield, with an observed 82% ee (Scheme 1.9).



Scheme 1.9. *Enantioselective β-boration of cinnamonitrile **12**.*

Once it has been shown that the enantioselective β-boration could be achieved using chiral phosphine ligands, Yun et al. attempted the scope of this protocol and the influence of other chiral phosphine ligands with a series of α,β-unsaturated esters and nitriles (Table 1.2)[37-39]. All the ligands that were screened induced enantioselectivity; however, it is clear from looking at Table 1.2, that Josiphos and Mandiphos (**L3** and **L4** respectively) showed the most promising results concerning to asymmetric induction (Table 1.2, entries 1, 2).

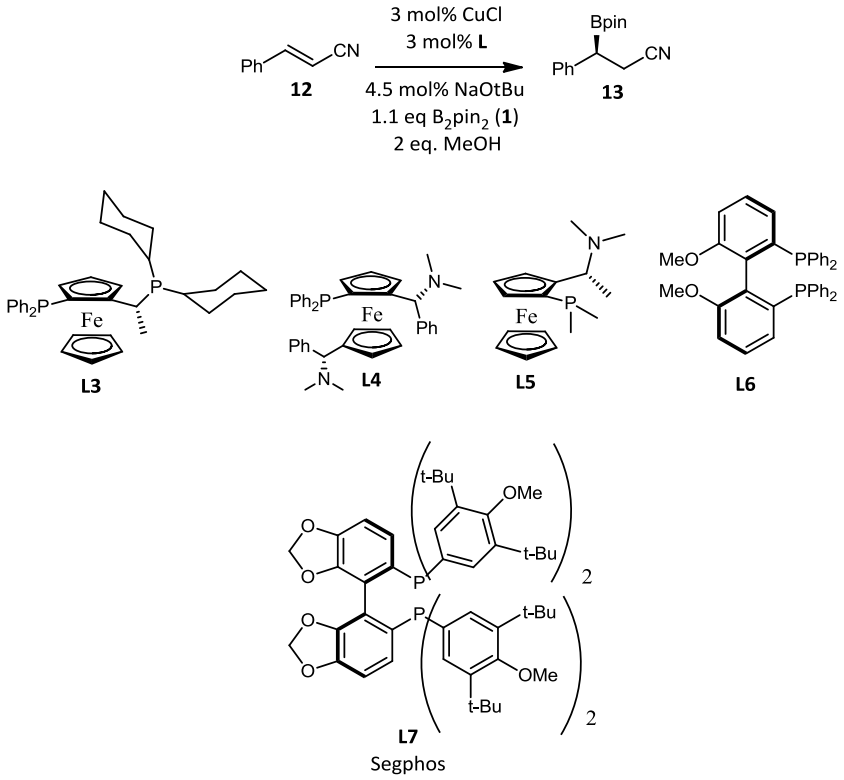


Table 1.2. *Enantioselective β-boration of α,β-unsaturated esters and nitriles.*

Entry	Ligand	Yield(%)[a]	ee(%)[c]
1	**L3**	97	94
2[b]	**L4**	96	94
3	**L5**	93	55
4	**L6**	92	3
5	**L7**	92	80

[a]*Isolated yield.* [b]*NaOtBu (3 mol%).*[c]*ee calculated on the β-borated product*

Once demonstrated that **L3** and **L4** were the best in terms of conversion and enantioselection, they both were employed in the enantioselective β-boration-oxidation sequence of a series of α,β-unsaturated esters and nitriles (Table 1.3). This protocol also resulted in high yields and high levels of enantioselectivity across a wide range of substrates (Table 1.3), with **L3** providing a higher level of enentioselectivity than **L4** (Table 1.3, entries 4 *vs.* 5 and 8 *vs*. 9). Yun et al. also made interesting observations regarding β-substituent effects, electron withdrawing group influence and ester moiety effects on the asymmetric induction of the screened reactions. Potential β-substituent effects on enantioselectivity can be examined by comparing entries 1-6 and 11-13 (Table 1.3), where the substrates differ only by their β-substituents. The β-

substituents differ in terms of both steric and electronic effects in each case and the observed ee values were remarkably similar, which suggested that the β-substituent did not have a dominant effect on the enantioselectivity of the reaction.

The nature of the electron withdrawing group (ester or nitrile in this case) was found to have an influence on the enantioselectivity (Table 1.2 entry 2 and Table 1.3 entry 5). When the electron withdrawing group was the α,β-unsaturated nitrile, this resulted in higher enantioselectivity (94% ee) compared to the analogous ester (87% ee). Having established that the nature of the electron withdrawing group plays an important role in stereoselectivity, Yun et al. examined this further in the case of esters by varying the alkoxy substituent on the ester. They found that changing the alkoxy substituent from simple methoxy group to more sterically demanding substituent (OtBu) gave no observable effect on the enantioselectivity.

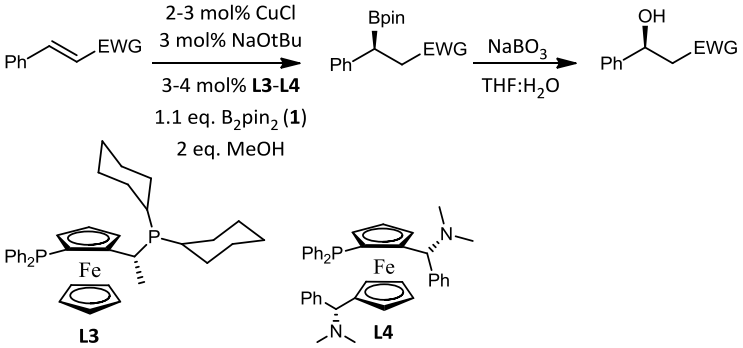
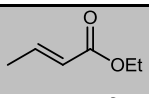
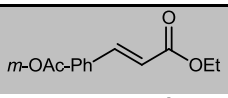
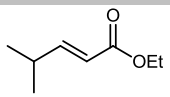
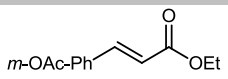
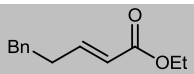
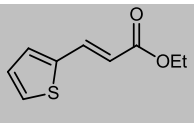
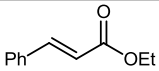
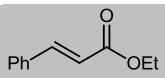
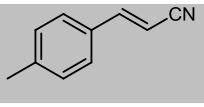
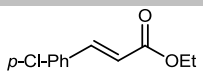
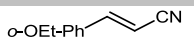
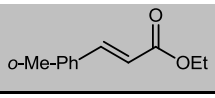
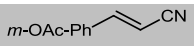


Table 1.3. *Enantioselective β-boration/ oxidation of α,β-unsaturated carbonyl compounds.*

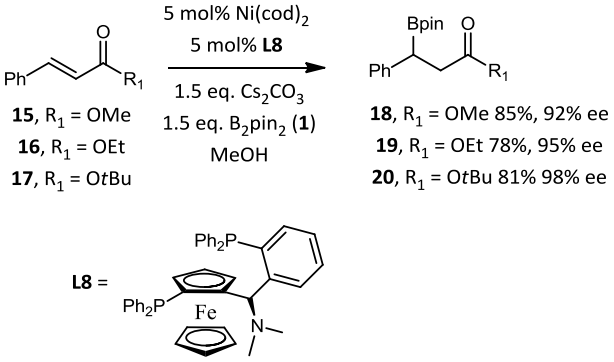
Entry	Substrate	Yield (%)[a]	ee (%)[b]	Entry	Substrate	Yield (%)[a]	ee (%)[b]
1		94[c]	90(R)	**8**		95[c]	87
2		92[c]	91(S)	**9**		89[d]	84
3		97[c]	89	**10**		93[c]	82
4		93[c]	90(S)				
5		94[d]	87(S)	**11**		94[c]	90(S)
6		90[c]	91(S)	**12**		90[c]	92
7		87[c]	88	**13**		94[d]	91

[a]Isolated yield of β-boration product. [b]ee of the oxidized product. [c]CuCl (2 mol%), NaOtBu (3 mol%), **L3** (4 mol%). [d]CuCl (3 mol%), NaOtBu (3 mol%), **L4** (3 mol%).

Interestingly, Fernández et al. explored the nickel and palladium catalyzed enantioselective β-boration of α,β-unsaturated esters[40], having previously explored the asymmetric β-boration of α,β-unsaturated esters using a copper catalyst, furnished with chiral N-heterocyclic carbenes (NHC)[41,42].

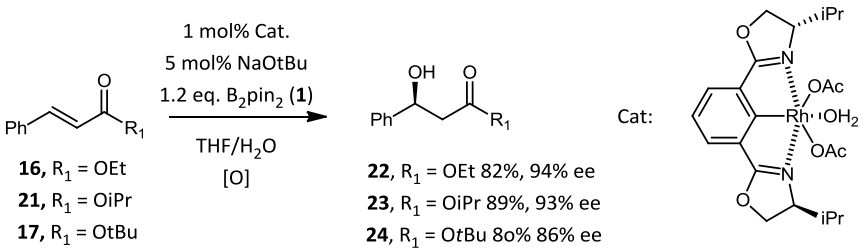
In light of the previously mentioned work of Yun et al.[38], Fernández et al. used a nickel catalyst system to examine whether the enantioselectivity of the catalytic β-boration was indeed independent of ester variation and found that the ester moiety was influencing the

enantioselectivity of the reaction (Scheme 1.10). This feature was observed across a range of different chiral ligand systems and the trends were similar in each case, i.e. from OMe to OiBu, the asymmetric induction increased with greater steric bulk on the ester moiety. It is important to note that the same trend was also observed in the palladium-catalyzed system, also developed by Fernández et al[40].



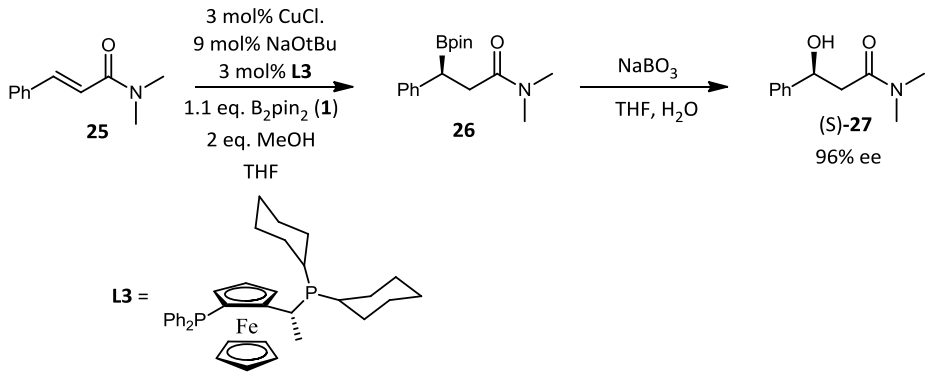
Scheme 1.10. *Enantioselective Ni-catalyzed borylation of α,β-unsaturated esters.*

Later on, Nishiyama et al.[43] examined the effect of the ester on enantioselectivity and found an inverse trend to that reported by Fernández et al[40]. The rhodium-catalyzed β-boration had been reported previously[32], however, an asymmetric protocol for the β-boration had yet to be established. Nishiyama developed a rhodium catalyst that employed a chiral bisoxazolinylphenyl ligand to induce enantioselectivity in the β-boration (Scheme 1.11). Nishiyama et al. found that by increasing the steric bulk of the ester moiety, a decrease in enantioselectivity was observed, moreover, with different rhodium-bisoxazolinylphenyl systems, the same trend of decreased enantioselectivity with more sterically demanding esters was observed.



Scheme 1.11. *Rhodium catalyzed asymmetric β-boration of α,β-unsaturates esters.*

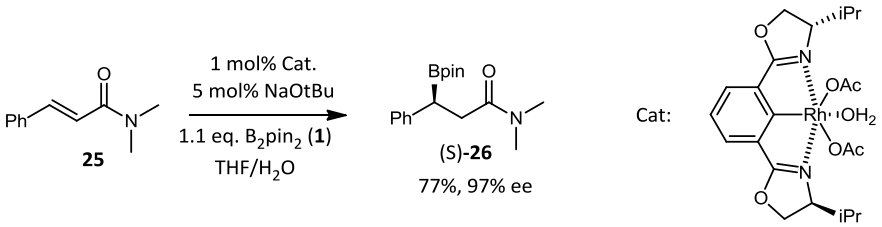
The work by Yun et al. was highly influential as it stablished for the first time a protocol for enantioselective β-boration that could be applied to a broad range of substrates. Yun et al. explored the β-boration of α,β-unsaturated amides as this was another way of gauging the influence of the electron withdrawing group, and to expand the substrate scope of this protocol[38](Scheme 1.12).



Scheme 1.12. Copper *catalyzed β-boration of α,β-unsaturates amides.*

Oshiyama et al. had previously developed an efficient nickel catalyzed protocol for the β-boration of α,β-unsaturated esters and amides[44]. Yun et al. extended their previously established enantioselective boration protocol from α,β-unsaturated esters and nitriles to the analogous α,β-unsaturated amides. The previous protocol could not be directly applied due to the α,β-unsaturated amides being poorer Michael acceptors compared to the analogous α,β-unsaturated esters and nitriles which resulted in conversions as low as 23%. Unlike their previous examples involving the enantioselective β-boration of α,β-unsaturated esters and nitriles, the system for the α,β-unsaturated amides is limited to a few substrate variants.

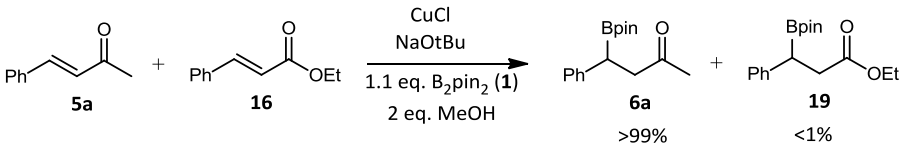
Nishiyama et al. also reported a route to α,β-unsaturated amides via a chiral rhodium-bisoxazolinphenyl system[43], giving the β-borated amide in good yield and excellent ee (Scheme 1.13). The extension of this work has also been studied[45]. Interestingly, Molander et al. also reported a method of β-boration of α,β-unsaturated amides using tetrahydroxydiborane[46]. They were able to explore the asymmetric version several years later[47].



Scheme 1.13. Rhodium *catalyzed asymmetric β-boration of α,β-unsaturates amides.*

Exploration into the metal-catalyzed enantioselective β-boration of α,β-unsaturated esters, nitriles and amides is complex. It offers great insight into the mechanistic pathways that undergo this reaction. However, points of disagreement regarding what influences the enantioselectivity have arisen. It is clear that the electron withdrawing group (ester, nitrile or amide) does play a dominant role in asymmetric induction, however, the β-substituent and ester moiety effects also play a subtle role in asymmetric induction, a role that is not fully understood.

The inherent reactivity of the copper catalyzed protocols of Hosomi and Miyaura et al[27-29] meant that asymmetric induction was a challenge, even with the use of chiral phosphine ligands. This allowed the exploitation of potential enantioselective pathways in the β-boration of α,β-unsaturated ketones[34]. This potential was explored by Yun et al. on the enantioselective β-boration of acyclic α,β-unsaturated ketones[48]. The crucial role of methanol was demonstrated in the β-boration reaction of two analogous α,β-unsaturated compounds (**5a** and **16**, Scheme 1.14). They combined two α,β-unsaturated carbonyl species and reacted them in parallel, by means of examining the reactivity of the α,β-unsaturated ketone **5a** relative to previously explored α,β-unsaturated ester **16**.



Scheme 1.14. Reactivity towards β-boration of α,β-unsaturates compounds.

Interestingly, they found that under these conditions, the β-boryl ketone **6a** was formed in near quantitative conversion, whereas the analogous ester **19** was formed in very low yields (<1%). The above reaction (Scheme 1.14) was achieved without the presence of a ligand and, therefore, Yun examined whether asymmetry could be induced using chiral phosphine ligands (**L3** and **L4**) in the presence of alcohol additives (methanol, isopropanol or *tert*-butanol) in varying amounts (1-2 eq.). Those attempts resulted in excellent conversion (92-100%) and moderate to good levels of asymmetric induction (37-80% ee). Interestingly, even without the addition of alcohol additives, high levels of asymmetric induction were achieved (56-77% ee). However, the alcohol free reactions did not proceed to completion and poorer yields were typically observed (18-54%).

Having established and gained an understanding of the parameters which influence both enantioselectivity and conversion, Yun et al[48]. expanded this methodology further by testing various substrates using both **L3** and **L4** and different alcohol additives (Table 1.4). In light of the experimental evidence shown in Table 1.4, Yun et al. observed that methanol was the more effective alcohol additive, typically leading to greater levels of conversion and improved enantioselective control. Again, as in the case of α,β-unsaturated esters and nitriles[38], the β-substituent induced subtle changes on the degree of conversion and enantioselectivity of the reaction. Even though it is worth noting that β-substituents do indeed influence these parameters, it is difficult to deduce with certainty if there is any trend between β-substituents and enantioselectivity. It is clear that **L3** is certainly more influential in asymmetric induction when compared to **L4**.

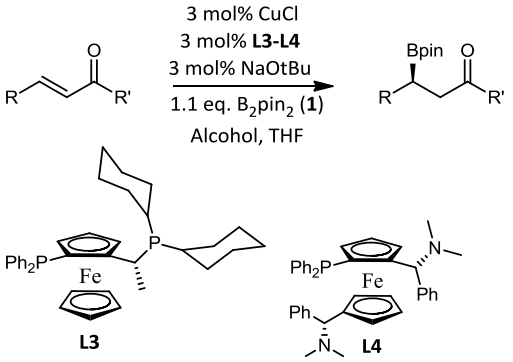
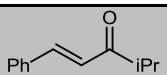
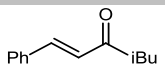
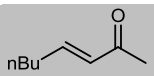
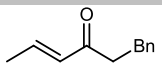
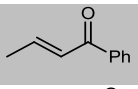
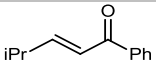
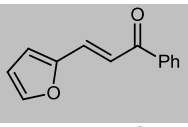
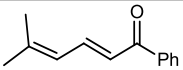


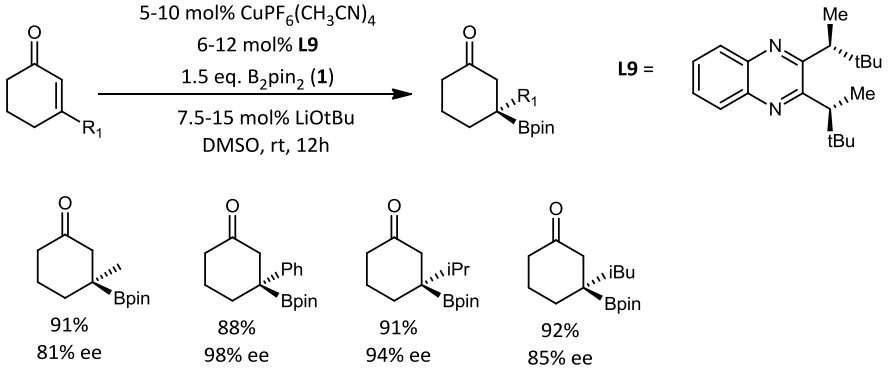
Table 1.4. *Enantioselective β-boration of ketones.*

Entry	Substrate	Ligand	Alcohol	Yield(%)[a]	ee(%)[b]
1		**L3**	iPrOH	94	95
2		**L3**	MeOH	97	89
3		**L4**	MeOH	93	93
4		**L3**	MeOH	89	81
5		**L4**	MeOH	91	88
6		**L3**	MeOH	93	90
7		**L4**	MeOH	86	30
8		**L3**	MeOH	95	90
9		**L3**	iPrOH	90	88
10		**L4**	MeOH	96	30
11		**L3**	MeOH	97	97
12		**L3**	MeOH	94	97
13		**L3**	MeOH	72	91
14		**L3**	iPrOH	72	9
15		**L3**	MeOH	93	96
16		**L3**	iPrOH	70	95

[a]Isolated yield. [b]Calculated from the corresponding β-hydroxy ketone.

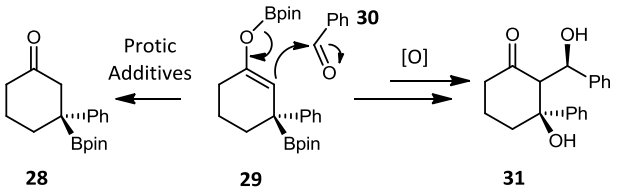
β,β-Disubstituted electron-deficient alkenes are particularly challenging in terms of asymmetric synthesis. This is due to the increased difficulty in enantio-differentiation between β,β-disubstituents on conjugate addition, when compared to regular mono-β-substituted species. To overcome this problem, Shibasaki et al[49] presented a communication in 2009

which reported an efficient and enantioselective methodology for the β-boration of β,β-disubstituted enones (Scheme 1.15).



Scheme 1.15. *β-boration to cyclic β,β-disubstituted α,β-unsaturated species.*

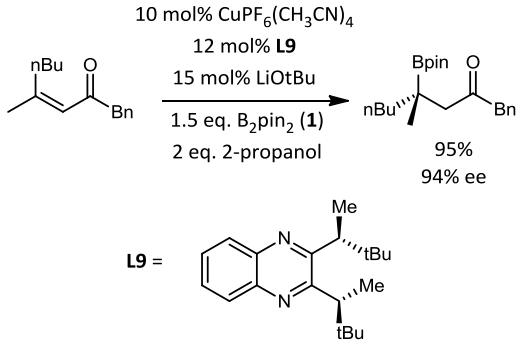
Interestingly, their optimized conditions did not require alcohol additives and made use of an unexplored, in boron conjugate addition, chiral diphosphine ligand **L9**. The substrate scope of this system was probed on cyclic α,β-unsaturated ketones. All substrates were obtained in excellent enantioselectivity and high yield. Shibasaki et al. also demonstrated the potential for stereoselective aldol-type reaction between the 1,4-diborated intermediate **29** and benzaldehyde **30**. This was possibily due to the lack of protic additives quenching the intermediate boron enolate (Scheme 1.16). The lack of alcohol additives provided a greater scope of application of the reaction. Not only was it possible to introduce one boron substituent enantioselectively, but also this showed that multiple stereocenters could be controlled in one-pot. This work overcame some limitations associated with the conjugate addition of boron to β,β-disubstituted α,β-unsaturated species[49].



Scheme 1.16. *Aldol product formed via intermediate enolate.*

Both Hoveyda et al. and Shibasaki et al. demonstrated that the enolate intermediate can serve as a suitable nucleophile, functionalizing the Cα-position stereoselectively. The analogous intramolecular reaction was exploited by Lam et al., which resulted in the formation of highly cyclic products, with high stereocontrol and functionality[50].

Limited not only with a protocol concerning the β-boration of cyclic β,β-disubstituted α,β-unsaturated carbonyl compounds, Shibasaki et al. developed a protocol for the corresponding acyclic β,β-disubstituted α,β-variants (also shown by Yun et al.[48]) using an adaptation of their protocol for cyclic species[51]. This produced some excellent results, with reaction conversions ranging from 71-95%, with equally high levels of stereocontrol (Scheme 1.17).



Scheme 1.17. *Shibasaki's β-borylation for linear β,β-disubstituted α,β-unsaturates ketones.*

Most of the literature regarding β-boration is based on the conjugate addition of boron to activated alkenes, typically activated by carbonyl electron-withdrawing moieties, such as amides, ketones and esters[52]. Alkenes activated by nitriles are present in the literature, but α,β-unsaturated imines are under-explored since α,β-unsaturated imines can be challenging to prepare and purify[53-55]. However, they offer scope for boron conjugate addition (functionalization at the β-carbon), and via exploitation of the imine functionality leading to 1,3-difunctionalization[56]. In addition, the previous examples of enantioselective β-boration, and the elegant methods for substrate controlled asymmetric induction[57], offered considerable potential for controlling multiple stereocenters in simple organic species. To this end, Fernández and Whiting et al. examined whether α,β-unsaturated imines **32** could serve as a suitable platform for a novel asymmetric route to γ-amino alcohols[58,59]. Other asymmetric routes to γ-amino alcohols exist[60], however, Fernández and Whiting et al. explored the previously established methods of boron conjugate addition, more specifically the asymmetric variant, by means of enantioselectively introducing a boryl substituent at the β-position of the

α,β-unsaturated imine substrate (Table 1.5). Interestingly, the resulting β-boryl imine **33** species would be ideally placed for remote asymmetric reduction[61,62]. This potential, coupled with established methods for the stereospecific oxidation of boron-containing substituents was an intriguing concept that needed to be explored. Hence, Fernández and Whiting et al. examined this concept by asymmetric copper-catalyzed β-boration of α,β-unsaturated imines **32**[58]. This involved the screening of multiple chiral phosphine ligands by means of devising an efficient protocol for the preparation of chiral β-boryl imines. All the Cu(I)/ligands that were screened induced asymmetry, and moreover, some of the Cu(I)/ligands gave the β-boryl imines in excellent conversion and enantioselection (Table 1.5).

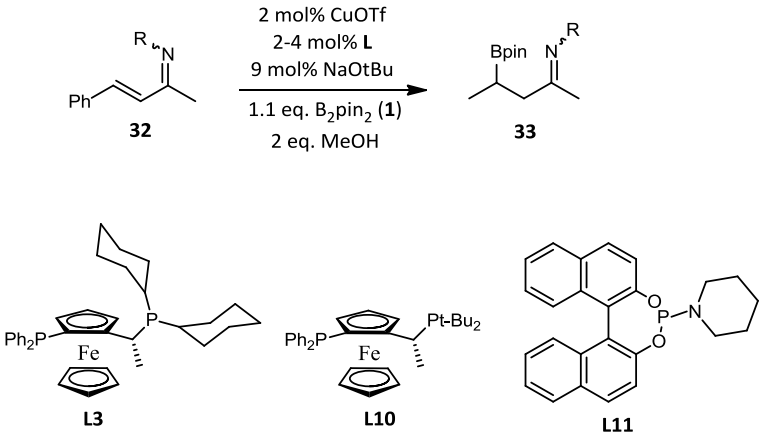
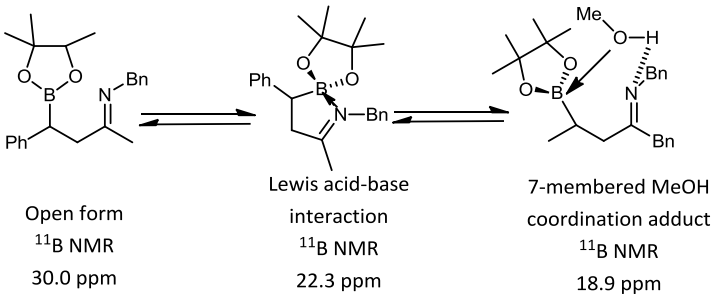


Table 1.5. *Enantioselective β-boration of α,β-unsaturated imines.*

Entry	R	Ligand	Conversion(%)[a]	ee(%)[b]
1	Ph	**L3**	61	63
2	Ph	**L10**	66	30
3	Ph	**L11**	>99	95
4	Bn	**L3**	>99	91
5	Bn	**L10**	>99	77
6	Bn	**L11**	>99	75

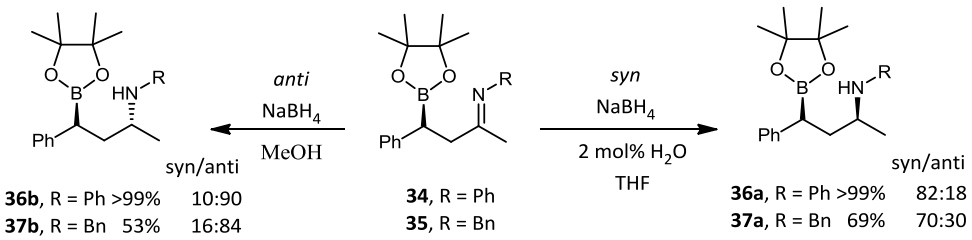
[a]Deduced using ^{1}H NMR spectroscopy.[b]Determined by GC analysis.

Next, they turned their attention to the asymmetric reduction of the imine functionality. They observed an intramolecular Lewis acid-base interaction (B-N) indirectly by ^{11}B NMR spectroscopy (Scheme 1.18) which offered potential for the exploitation of previously established reduction methodologies[61,62].



Scheme 1.18. *11B NMR evidence for intramolecular Lewis-acid base interaction.*

Indeed, on screening various reducing agents and proton sources, they discovered means of asymmetrically reducing the imino functionality, and by solvent modification, could tune the selectivity between *syn*- and *anti*-diaestereomer formation (Scheme 1.19). This protocol was achieved in a one-pot synthesis, by which the β-boration, imine reduction and boronate oxidation could be carried out consecutively. This methodology brought together asymmetric conjugate boration and remote stereoselective reduction, and established a protocol to access γ-amino alcohols with high levels of stereocontrol across multiple stereocenters. Shortly after this, the protocol was extended to the preparation of γ-hydroxy alcohols and a wider substrate base for the previously established γ-amino alcohols[63].

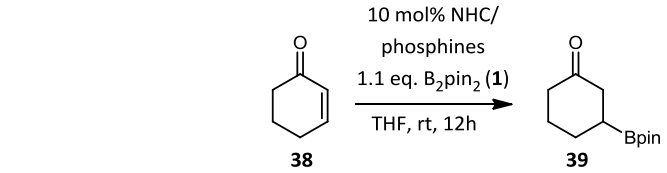


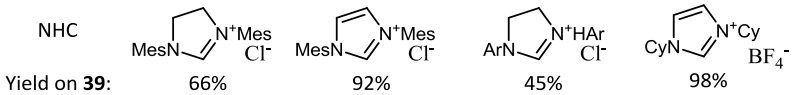
Scheme 1.19. *Tuneable diaestereocontrol by solvent modification.*

1.3 Asymmetric organocatalytic β-boration

Enantioselective transition metal-catalyzed β-boration has received considerable attention in the literature due to the efficiency, in both conversion and high levels of asymmetric induction, especially in copper-catalyzed systems. However, organocatalysis[64] has had a reinassance in recent years, in part due to the work of Barbas and List et al.[65] and MacMillan et al[66]. Such methods have probed to be highly creative, but also show novel modes of activation and catalysis that can be achieved from such systems[67]. It is perhaps no surprising that such organocatalytic protocols have been developed and applied to the β-boration of electron-deficient alkenes.

The first example of an organocatalytic β-boration methodology was reported by Hoveyda et al. in 2009[68]. Hoveyda developed the first procedure for the β-boration of both cyclic and acyclic α,β-unsaturated ketones. This breakthrough made use of an organic system consisting of N-heterocyclic carbenes (NHCs) in substoichiometric loadings. It should be noted that Sadaghi et al. had previously isolated NHC-Cu-Bpin species[69] and had demonstrated its efficiency to alkene insertion[70]. Hoveyda et al. examined this by taking cyclic α,β-unsaturated ketones and probing the β-boration of this species with various NHC and phosphine salts. Surprisingly, addition of the catalytic amounts of NHC to a solution of the α,β-unsaturated ketones and diboron reagent **1** resulted in moderate to excellent yields of the β-boration products (Scheme 1.20).





Ar = 2,6-di-isopropylphenyl

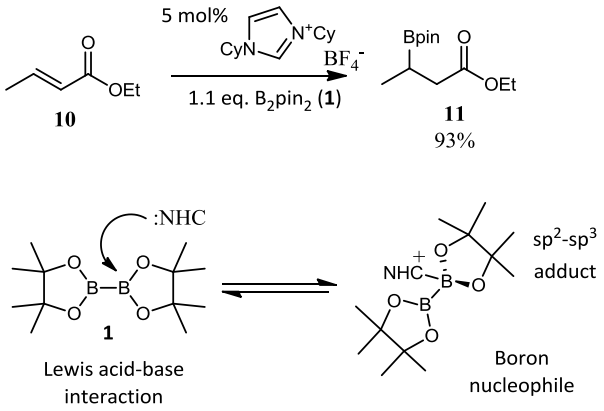
Phosphines	PPh_3	$OPPh_3$
Yield on **39**:	<2%	50%

Scheme 1.20. *The examined catalytic species in the β-boration of cyclic enones.*

Moreover, this protocol was applied to both endo- and exo-cyclic α,β-unsaturated ketones, giving excellent yield (88-98%). This protocol could even be extended to cyclic α,β-unsaturated

esters showing equally excellent yields up to 95%. Interestingly, the catalytic activity of phosphine oxide gave the corresponding β-boryl ketone in moderate yield (50%) without the presence of a transition metal or NHC to facilitate boration. This had been observed before by Hosomi, but overall conversion was considerably poorer (7%)[27].

To explain the observed organocatalytic behavior of the NHCs, Hoveyda et al. postulated an in situ interaction between the Lewis acidic diboron (e.g. B_2pin_2 **1**) and the nucleophilic (Lewis base) NHC (Scheme 1.21). Furthermore, it was suggested that this resulted in a nucleophilic boron species that could undergo conjugate addition to the α,β-unsaturated ketones.



Scheme 1.21. *Hoveyda's proposed nucleophilic adduct in the β-boration of electron-deficient alkenes.*

The introduction of a non-metal-catalyzed protocol for the β-boration of α,β-unsaturated species was a useful contribution to the area. It raised questions regarding the mechanistic understanding of these types of processes, especially the role of the phosphine ligands. This research was extensively explored by Fernández and Gulyás et al. who in 2010, introduced the first phosphine-based organocatalytic enantioselective β-boration of α,β-unsaturated species[71]. This has subsequently been explored by Hoveyda et al. using chiral NHCs[72]. Fernández et al. knew from the early work of Hosomi et al. that phosphines in the absence of transition metal salts had the ability to facilitate boron conjugate addition to α,β-unsaturated species. Moreover, chiral phosphine ligands had been shown in numerous examples to induce enantioselectivity with respect to the β-boration of prochiral activated alkenes in the presence of transition metal salts[73]. First, they tested the ability of various achiral phosphines, bases and alcohols, with the aim of facilitating the β-boration of ethyl crotonate **10** (Table 1.6).

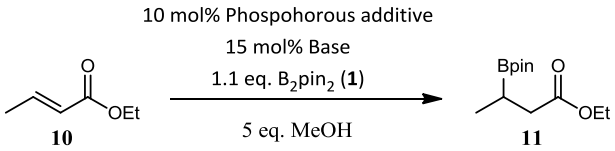


Table 1.6.*Testing the catalytic potential of phosphines towards borylation.*

Entry	Phosphorous Additive	Base	Alcohol	Conversion(%)[a]
1	PPh_3	-	MeOH	0
2	PPh_3	Cs_2CO_3		12
3	PPh_3	Cs_2CO_3	iPrOH	49
4	PPh_3	Cs_2CO_3	MeOH	99
5	$OPPh_3$	Cs_2CO_3	MeOH	21
6	DPPF	Cs_2CO_3	MeOH	39

[a]Deduced using GC analysis. Confirmed using ^{1}H NMR spectroscopy.

Surprisingly, a variety of phosphorus compounds facilitated the β-boration of ethyl crotonate in reasonable to excellent yields. The addition of base was found to be crucial for the β-boration, and of the bases that were explored (CsF, NaOtBu, K_2CO_3 and Cs_2CO_3) Cs_2CO_3 was the most successful. Now that the non-metal-catalyzed protocol had been optimized for ethyl crotonate, Fernández et al. aimed to explore the asymmetric potential of this reaction through the use of chiral phosphine ligands[71]. This was done by probing a series of chiral ligands in the β-boration of ethyl crotonate **10** (Table 1.7)

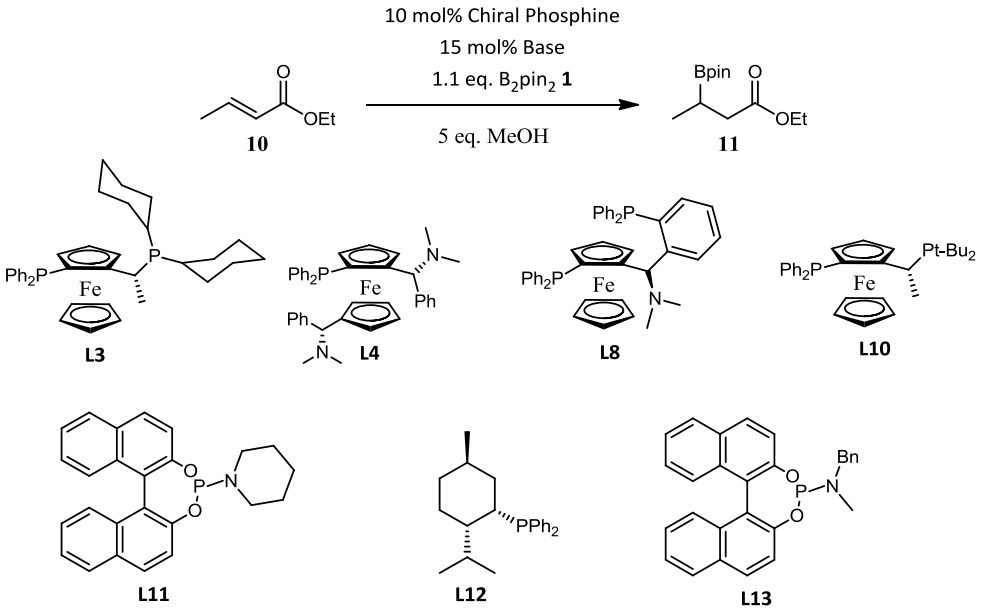


Table 1.7.*Chiral phosphine testing for the developing of asymetric organocatalytic β-boration protocol.*

Entry	Phosphine	Base	Conversion(%)[a]	ee(%)
1	**L3**	Cs_2CO_3	99	75(S)
2	**L4**	Cs_2CO_3	58	<5
3	**L8**	Cs_2CO_3	64	72(S)
4	**L12**	Cs_2CO_3	74	<5
5	**L11**	Cs_2CO_3	53	7(R)
6	**L13**	Cs_2CO_3	54	35(S)
7	**L10**	Cs_2CO_3	94	88(S)
8	**L10**	NaOtBu	59	55(S)
9	**L10**	CsF	72	89(S)

[a]Calculated by GC analysis, confirmed using ^{1}H NMR spectroscopy.

Initially, **L12** was examined as a potential ligand for inducing enantioselectivity in the reaction. High conversions were observed with the chiral monophosphine, but it only provided minimal enantioselectivity (< 5%, Table 1.7 entry 4). The phosphoramidites **L11, L13** on the other hand gave poorer conversions, but induced enantioselectivity. However, the more effective phosphines at inducing enantioselectivity probed to be Taniaphos (**L8**) and the Josiphos (**L3** and **L10**) type species (Table 1.7).

This demonstrated for the first time that asymmetric β-boration doesn't need to be carried out using metal catalysts with chiral ligands, on the contrary, chiral phosphine, base and a suitable alcohol additive alone, were sufficient to provide enantioselectivity in the conjugate addition of boron to α,β-unsaturated carbonyl compounds. However, this protocol was limited to ethyl crotonate **10** and therefore, Fernández et al. needed to demonstrate that this procedure could also be applied to various other substrates[71]. This was explored using the same substrates as explored in the racemic case. This protocol was found to be applicable to a wide range of substrates (Figure 1.2) and probed highly effective in terms both of conversion and enantioselectivity. The Josiphos ligand **L10** probed to be the most successful phosphine additive (Figure 1.2). Both cyclic and acyclic α,β-unsaturated ketones and esters were explored, the β-boration products of which showed reasonable to high levels of enantiopurity (36-83%).

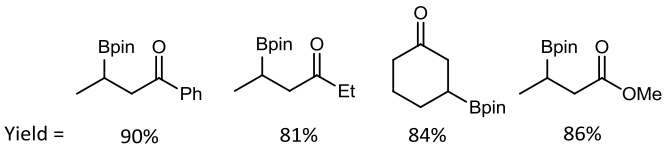
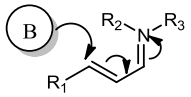


Figure 1.2. *Products of Fernández et al.'s organocatalytic β-boration protocol.*

The utility of the process was clearly demonstrated by the encouraging results, however, it raised questions regarding the underlying mechanistic principles of the reaction. Building on their previous work, Fernández and Gulyás et al. explored their newly devised non-metal-catalyzed route to the β-boration of α,β-unsaturated carbonyl compounds, and examined the role of iron as an additive by means of assisting this process[74], demonstrating the preactivation of the substrate by Fe(II) salts.

As previously mentioned, organocatalysis has had a renaissance in recent years. A tremendous amount of work has been published on the use of secondary amines and their roles in the

catalytic activation of α,β-unsaturated aldehydes and ketones (iminium activation) towards conjugate addition[67]. To this end, Córdova et al. presented their work in 2012 on the organocatalytic β-boration of enals, catalyzed by a combination of Lewis base (for activation of the diboron reagent) and secondary amines (to activate the substrate)[75](Figure 1.3).



Iminium activation

Figure 1.3. *Organocatalytic modes of activation in the β-boration reaction throughout iminium activation.*

The initial products were trapped in situ by phosphorus ylides to generate homoallyl boronates. They had previously reported a copper-catalyzed enantioselective protocol, where enantioselectivity was achieved through the use of a chiral secondary amine additive[76].

1.4 Catalytic β-boration in aqueous media

Transition metal catalysis often requires anhydrous, oxygen-free conditions to prevent catalytic degradation. But in recent years, water has become an attractive medium to perform interesting reactions, not just because of its huge abundance and environmentally benign properties, but also because of its influence on chemical reactions[77].

It is therefore interesting to report the findings of Kobayashi et al. who reported the first copper-catalyzed enantioselective protocol for the β-boration of α,β-unsaturated carbonyl compounds in aqueous media[78]. It is important to note that in the same year Santos et al. reported the first copper catalyzed β-borylation under aqueous conditions[79].

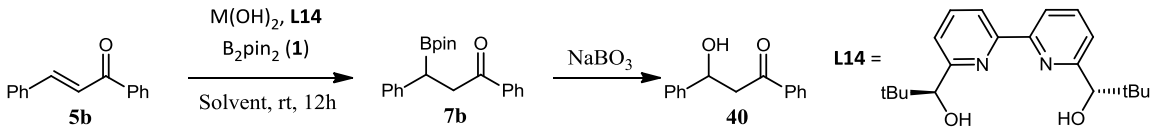


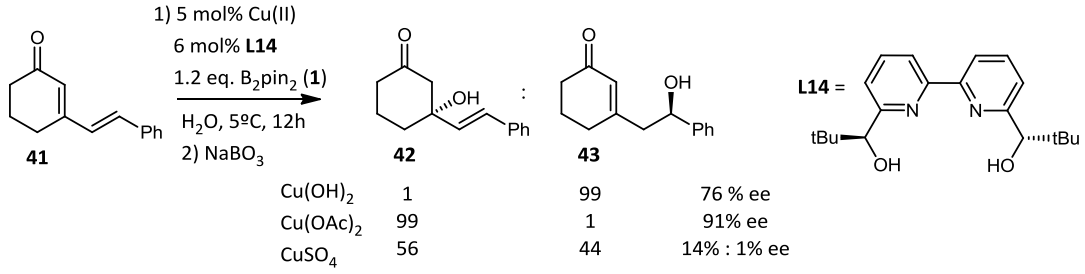
Table 1.8. *Kobayashi's methodology for borylation with $M(OH)_2$ in water.*

Entry	M	Solvent	Additive	L	Yield(%)	ee(%)
1	Cu	H_2O	-	DBA	88	0
2	Zn	H_2O	-	DBA	64	0
3	Cu	H_2O	-	**L14**	83	81
4	Zn	H_2O	-	**L14**	17	46
5	Cu	H_2O	-	**L14**	79	36
6	Cu	H_2O	-	**L14**	80	37
7	Cu	THF	-	**L14**	0	0
8	Cu	Toluene	-	**L14**	0	0
9	Cu	DCM	-	**L14**	0	0
10	Cu	DMF	-	**L14**	Trace	0
11	Cu	DMSO	-	**L14**	0	0
12	Cu	MeOH	-	**L14**	17	29
13	Cu	EtOH	-	**L14**	1	0
14	Cu	H_2O	-	**L14**	84	80
15	Cu	H_2O	Pyridine	**L14**	72	70
16	Cu	H_2O	AcOH	**L14**	93	89
17	Cu	H_2O	TFA	**L14**	93	86
18	Cu	H_2O	$PhCO_2H$	**L14**	86	81
19	Cu	H_2O	$B(OH)_3$	**L14**	94	87
20	Cu	H_2O	AcOK	**L14**	90	81
21	Cu	H_2O	AcOH	**L14**	95	99

Entries: 1-13, $M(OH)_2$ = 10 mol%; 14-21 $M(OH)_2$ = 5 mol%. Optimized conditions for Entry 21 uses **L14** (6 mol%) at 5ºC for 12h.

The procedure offered great potential due to the availability of the copper (II) salt precursor, chiral bipyridine **L14** and water with some additives (Table 1.8). They demonstrated that this could be applied to α,β-unsaturated amides, esters and ketones. Moreover, the more challenging β,β-disubstituted enones could be β-borylated in high ee (93-97%) and conversion.

In addition, they examined the regioselectivity of this protocol by examining the α,β,γ,δ-unsaturated ketones within their methodology. To their delight, they found that this resulted in high regioselectivity, producing mainly the 1,4-addition product (96%) with excellent enantioselection (89%)[80,81]. Initially, they found the acyclic α,β,γ,δ-unsaturated ketones proceed to give predominantely the 1,4-addition product. However, the behavior of cyclic α,β,γ,δ-unsaturated ketones (e.g. **41**) was different, depending on the counter ion of the Cu(II) salt (Scheme 1.22)



Scheme 1.22. *1,4-vs 1,6-addition to cyclic $\alpha,\beta,\gamma,\delta$-unsaturated ketones.*

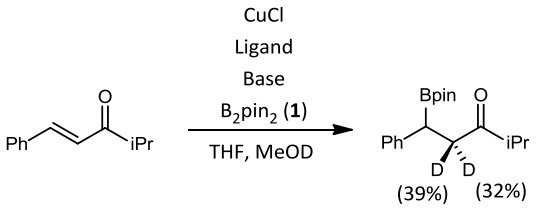
The modification of the counter ion, from hydroxide to acetate, allowed for the selective β-boration (1,4-addition) to γ-borylation (1,6-addition), respectively. Kobayashi et al. rationalized this by simple observation of the reaction, suggesting a switch from homogeneous catalysis in the case of $Cu(OAc)_2$, to heterogeneous catalysis with $Cu(OH)_2$. Further research was carried out in this area to elucidate the nature and mechanism of this reaction[81].

1.5 Mechanistic considerations

Marder et al. introduced the first example of 1,4-diboration to activated alkenes[19] which after hydrolysis, gave the corresponding β-boration product. Indirect evidence for 1,4-diboron species has been shown by other groups[82]. Indeed, they utilized the presumed 1,4-addition intermediate for the formation of aldol products. However, the formation of such species was thought to rely upon the presence of a nucleophilic boryl species, either if the reaction proceeds through an S_N2 or S_N2' type mechanism[83].

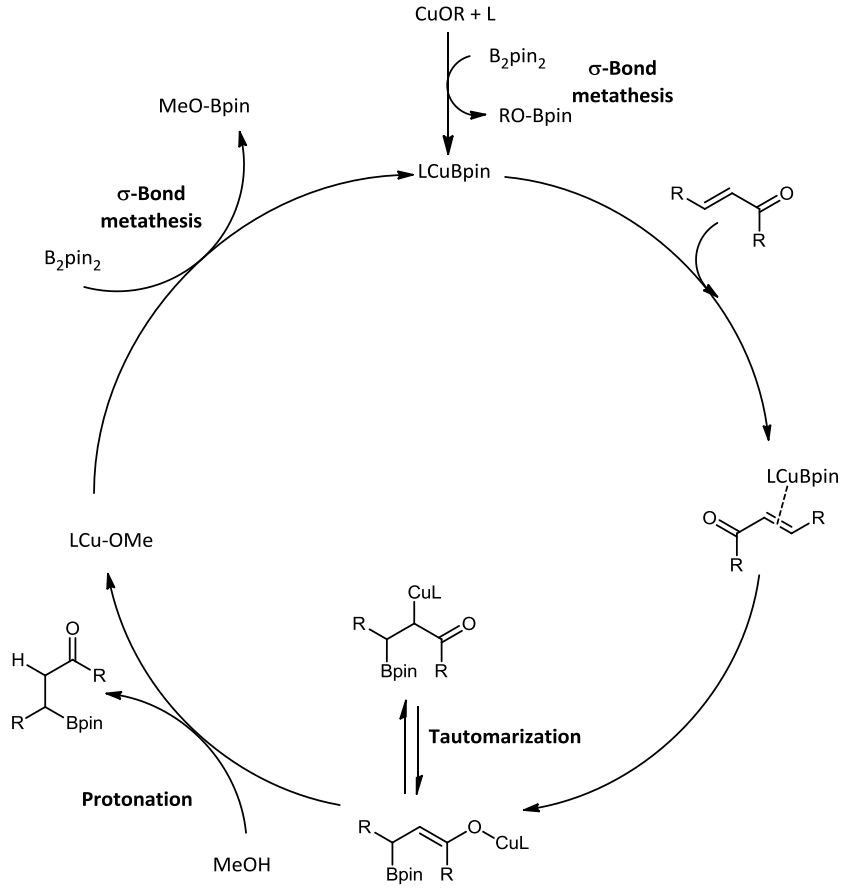
The initial copper-catalyzed examples of conjugate boration were performed using high catalyst loadings. The methodology of Yun et al. involved the use of protic additives that led them to speculate upon plausible mechanism and suggested that a diphosphine-ligated copper-boronate species[69], similar to the copper-boronate species suggested by

Miyaura[28], was key to the conjugate addition of the α,β-unsaturated carbonyl compounds. Furthermore, this results in either a C-bound copper intermediate or an O-bound copper enolate. Yun et al., suggested that the equilibrium between the C-bound and O-bound copper intermediates was favored towards the C-bound system. Accordingly, it would be this species that the alcohol additive would protonate. This suggested that this copper alkoxide was the active species involved in regenerating the active copper-boronate species. Yun et al., also provided evidence, in the form of isotopic labelling, for the protonation of the enolate intermediate, as shown in Scheme 1.23.



Scheme 1.23. *Isotopic labelling for the protonation intermediate.*

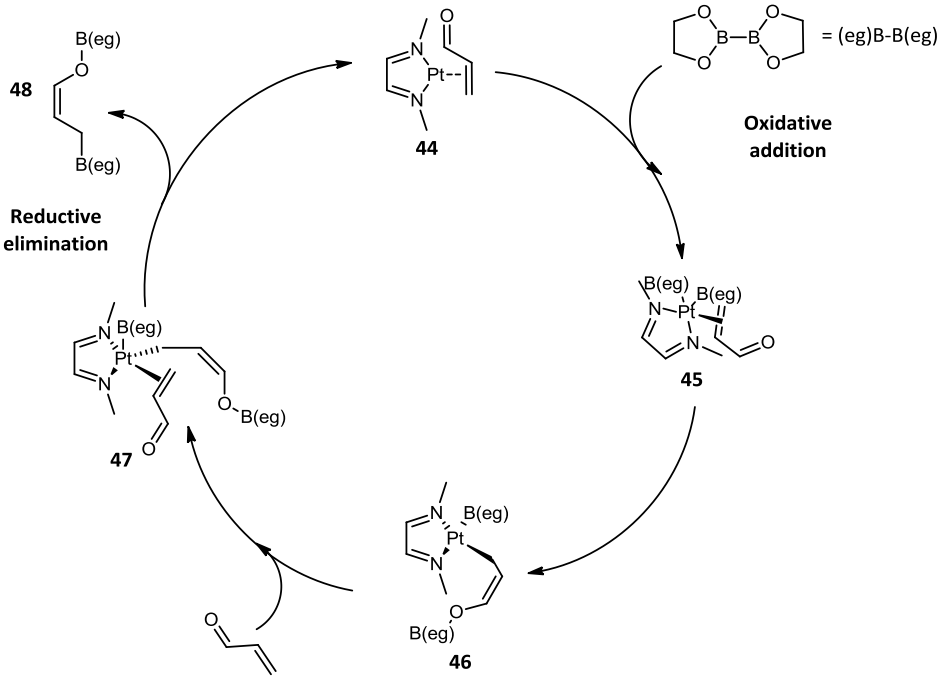
The groups of Marder and Lin et al., jointly carried out extensive DFT studies to try to elucidate some aspects of the underlying mechanistic implications of such reactions[83]. As part of this work, studies involving olefinic insertion to copper-boron bonds have been made[84] and therefore, led to the DFT study of the copper-catalyzed boron conjugate addition of activated alkenes[85]. Their findings support a mechanism similar to that outlined in Scheme 1.24, by which boration results in formation of a C-bound copper intermediate which could be protonated by the alcohol forming a copper alkoxide. Such process provides a barrier-less metathesis between such species and the diboron reagent. This work supported the suggested mechanistic pathway proposed by Yun[34].



Scheme 1.24.*Mechanism for the copper-catalyzed β-boration of α,β-unsaturated carbonyl compounds.*

Marder and Lin et al. performed DFT calculations on their original platinum catalyzed system[86]. Their initial calculations suggest that, unlike the copper-boron bond, in which electron density is located on boron (thus explaining its nucleophilicity), the platinum atom polarizes the platinum-boron bond towards itself, thus generating an electropositive boryl moiety. Subsequently, one cannot suggest a nucleophilic mechanism involving a catalytic platinum-boron species in the β-boration reaction. They have indeed shown, by DFT calculations and experimental observations, that the probable mechanism for the platinum catalyzed protocol occurs in three distinct steps (Scheme 1.25). The initial step in the reaction involves the oxidative addition of the diboron compound the to the platinum(0) species **44**. This intermediate is calculated to exhibit pseudo-trigonal-bipyramidal geometry **45**. Secondly, the conjugate addition of the electron rich platinum onto the β-carbon of the α,β-unsaturated carbonyl, acrolein, and the σ-bond formation between the carbonyl oxygen and the axial boryl moiety, leading to the formation of a square planar platinum species **46**. After this, re-coordination of the carbon-carbon double bond (in acrolein) to the platinum, results in the regeneration of a pseudo-trigonal-bipyramidal complex **47**. Finally, reductive elimination

results in the 1,4-addition product **48**, with the boryl units on the oxygen (of the enolate) and the β-carbon. In addition, interesting computational work by Carbó and Fernández et al. (in the same year) supported this idea of an electrophilic mechanism[87].



Scheme 1.25. *Mechanism for the platinum-catalyzed β-boration of α,β-unsaturated species.*

Concerning this subject, the mechanistic explanation appears comprehensive. However, the organocatalytic variants of metal-catalyzed boron conjugate addition cannot be understood in this framework and brings into question the role of the additives in such reactions. Hoveyda suggested a plausible concept by which the NHC species can generate a nucleophilic diboron adduct by the polarization of the boron-boron bond to form sp^2-sp^3 type species. Such species have since been isolated by Marder and Lin et al[88]. Hoveyda suggested that this adduct can react with the electrophilic β-carbon of the activated alkenes. However, Marder and Lin et al. also note that from their spectroscopic observations (^{11}B NMR), the association between the NHC and B_2pin_2 (**1**) was weak in solution, which raises doubt on this adduct being involved in the boron conjugate addition process. An interesting note in Hoveyda's methodology[68] is the trapping of enolate intermediates with aldehydes to form aldol like products (analogous work of Shibasaki et al[49]). Unlike the copper-catalyzed protocol, as reported by Shibasaki, the aldol products were equally formed with high levels of enantio- and diaestereo-control. However, under Hoveyda's organocatalysis the *syn*-diaestereomer was the dominant isomer,

unlike the copper catalyzed systems which have been reported to give the anti-diaestereomer[49].

Perhaps more interesting is that a phosphine oxide alone in the presence of B_2pin_2 (**1**) can facilitate boron conjugate addition (activation by the nucleophilic oxide coordinating to the diborane species). The ability of phosphines to be active in the metal free conjugate addition was noted by Hosomi et al.[27], but like Hoveyda et al., Hosomi did not explore this, despite the 50% conversion to the borylated species in the case of Hoveyda.

The organocatalytic β-boration, facilitated by phosphines, was probed by Fernández et al. to explore the underlying mechanism of such reactions[71].

Still alternative theories have been suggested to explain the role of the phosphines in the organocatalytic β-boration. Indeed, Fernández et al. reported other computational experimental data[90] which shows that the phosphines can undergo a 1,4-addition to the α,β-unsaturated carbonyl compounds (analogous to the Baylis-Hillman reaction[91]) which leads to the formation of an ion-pair intermediate (when in the presence of MeOH and the diboron compound **1**) that explains the catalytic behavior of such systems.

1.6 Summary

The area of boron conjugate addition (β-boration) is not only fascinating, but serves as a valuable synthetic utility for the preparation of simple organic building blocks that represent key structural moieties in many biologically active species and materials. Since the first examples appeared, transition metals have played a crucial role in facilitating this process. Platinum, rhodium and nickel have all been shown to facilitate boron conjugate addition, but perhaps due to the work of Yun et al., and use of alcohol additives, copper is now the most used catalytic system in the area. Recently, some groups have developed alternative methods by which β-boration can be achieved by organocatalytic means and they have obtained some excellent results. Such methodologies have not yet displayed results to compete with their metal-catalyzed equivalents, however, it is likely that these organocatalytic routes will develop with the use of additives, resulting in more sustainable chemical processes

A number of mechanistic theories have been put forward to explain the metal-catalyzed methodologies. In addition, mechanistic theories have been suggested to explain the organocatalytic reaction. Further developments are likely to be made in order to satisfactorily

explain all the observed results. To this end, further research is likely to be focused not only on developing new borylation systems, especially organocatalytic protocols and new asymmetric methods, but also on further mechanistic interpretations.

1.7 Scope and objectives of the thesis

Organoboron derivatives are important synthetic intermediates and biologically active compounds. In particular, boron conjugate addition to activated and unactivated alkenes has been proven to be an ideal mean of introducing boron functionalities to an alkene in a chemo-, regio-, and stereoselective manner. Despite the fact that the borylation reaction has gone through important improvements in the past years, there's still little knowledge and examples concerning one-pot reactions towards the obtantion of difunctionalized compounds utilizing boron conjugate addition methodologies in the case of α,β-unsaturated carbonyl compounds used as Michael acceptors.

We have focused along this thesis to develop novel chemical transformations related to the synthesis of difunctionalized compounds through borylation reactions.

Chapter 2 discusses a difunctionalization approach towards the obtantion of α-fluoro β-boryl ketones, in one pot, in a regio- and also enantioselective manner. To the best of our knowledge, the synthesis of those compounds are unprecedented.

Chapter 3 discusses a difunctionalization approach towards the obtantion of α-chloro β-boryl ketones and α-bromo β-boryl ketones, being those compounds also obtained in a regioselective manner and prepared for the first time in this work.

In *Chapter 4*, we describe the total synthesis of 2-aryl-1,3-diones through a one pot protocol that involves the formation of α-aryl-β-boryl ketones as a key intermediate. In this case we demonstrate the importance of such compounds as intermediates for organic synthesis and as an alternative route for the existing methodologies for the synthesis of 2-aryl-1,3-diones. Also, the synthesis of α-aryl β-boryl ketones has no precedent in the literature.

1.8 References

[1] a) E. L. Muetterties, *The Chemistry of Boron and Its Compounds* (John Wiley & Sons Inc., New York, **1967**); b) G. Hall, *Boronic Acids*; Wiley-VCH: Weinheim, Germany, **2005**; c) E. Fernández, A. Whitting, *Synthesis and Application of Organoboron compounds*. Springer. **2015**; d) L. Chausset-Boissaire, K. Ghozati, E. LaBine, J. L. –Y. Chen, V. K. Aggarwal, C. M. Crudden, *Chem. Eur. J.* **2013**, 19, 17698.

[2] C. M. Crudden, B. W. Glasspole, C. J. Lata, *Chem. Commun*. **2009**, 6704.

[3] The Nobel prize in Chemistry 1979. Last accessed March 2015: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/**1979**/

[4] H. C. Brown, *Hydroboration* W. A. Benamin, Inc., New York, **1962**.

[5] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett*. **1979**, *36*, 3437.

[6] G. A. Molander, L. Jean-Gérard, *J. Org. Chem.* **2009**, *74*, 1297.

[7] E. Fernández, M. W. Hooper, F. I. Knight, J. M. Brown, *Chem. Commun* **1997**, 173.

[8] S. N. Mlynarski, A. S. Karns, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 16449.

[9] a) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778; b) L. Ren, C. M. Crudden, *Chem. Commun.* **2000**, 721.

[10] D. A. Evans, T. C. Crawford, R. C. Thomas, J. A. Walker, *J. Org. Chem.* **1976**, *41*, 3947.

[11] H. C. Brown, M. W. Rathke, M. M. Rogie, *J. Am. Chem. Soc.* **1968**, *90*, 5038.

[12] H. C. Brown, C. F. Lane, *J. Am. Chem. Soc.* **1970**, *92*, 6660.

[13] H. C. Brown, W. R. Heydkamp, E. Breuer, W. S. Murphy, *J. Am. Chem. Soc*. **1964**, *86*, 3565.

[14] D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer-Verlag, Berlin, **1995**.

[15] E. Hupe, I. Marek, P. Knochel, *Org. Lett.* **2002**, *4*, 2961.

[16] R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, *Angew. Chem. Int.* Ed. **2011**, *50*, 3760.

[17] J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.* **2012**, *41*, 3558.

[18]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.

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

[20] T. B. Marder, N. C. Norman, *Top. Catal.* **1998**, *5*, 63.

[21] D. Männig, H. Nöth, *Angew. Chem. Int. Ed.* **1985**, *24*, 878.

[22] D. A. Evans, G. C. Fu, *J. Org. Chem.* **1990**, *55*, 5678.

[23] R. T. Baker, P. Nguyen, T. B. Marder, S. A. Westcott, *Angew. Chem. Int. Ed.* **1995**, *34*, 1336.

[24] a) T. Ishiyama, M. Yamamoto, N. Miyaura, *Chem. Commun.* **1997**, 689; b) T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc*. **1993**, *115*, 11018.

[25] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412.

[26] N. J. Bell, N. R. Cameron, A. J. Cox, S. O. Evans, T. B. Marder, M. A. Duin, C. J. Elsevier, X. Baucherel, A. A. D. Tulloch, J. R. P. Tooze, *Chem. Commun.* **2004**, 1854.

[27] H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821.

[28] K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2000**, 982.

[29] K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, *625*, 47.

[30] H. Ito, T. Ishizuka, J. Tateiwa, M. Sonoda, A. Hosomi, *T. J. Am. Chem. Soc.* **1998**, *120*, 11196.

[31] Y. Segawa, M. Yamashita, K. Nozaki, *Science* **2006**, *314*, 113.

[32] G. W. Kabalka, B. C. Das, S. Das, *Tetrahdron Lett.* **2002**, *43*, 2323.

[33] G. W. Kabalka, Z. Wu, M. Yao, *Appl. Organometal. Chem.* **2008**, *22*, 516.

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

[35] D. Kim, B. –M. Park, J. Yun, *Chem. Commun.* **2005**, 1755.

[36] G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253.

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

[38] J. Yun, Chapter 3. *Synthesis and Application of Organoboron Compounds*. E. Fernández, A. Whitting. Springer. **2015**.

[39] H. Chea, H. –S. Sim, J. Yun, *Adv. Synth. Catal*. **2009**, *351*, 855.

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

[41] V. Lillo, A. Prieto, A. Bonet, M. M. Díaz-Requejo, J. Ramírez, P. J. Pérez, E. Fernández, *Organometallics* **2009**, *28*, 659.

[42] V. Lillo, M. R. Fructos, J. Ramírez, A. A. C. Braga, F. Maseras, M. M. Díaz Requejo, P. J. Pérez, E. Fernández, *Chem. Eur. J.* **2007**, 13, 2614.

[43] T. Shiomi, T. Adachi, K. Toribatake, L. Zhou, H. Nishiyama, *Chem. Commun.* **2009**, 5987.

[44] K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2011**, *13*, 4684.

[45] K. Toribatake, L. Zhou, A. Tsuruta, H. Nishiyama, *Tetrahedron* **2013**, *69*, 3551.

[46] G. A. MOlander, S. A. McKee, *Org. Lett.* **2011**, *13*, 4684.

[47] G. A. Molander, S. R. Wisniewski, M. Hosseini-Sarvari, *Adv. Synth. Catal.* **2013**, *355*, 3037.

[48] X. Feng, J. Yun*, Chem. Eur. J.* **2010**, *16*, 13609.

[49] I. –H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki*, J. Am. Chem. Soc.* **2009**, *131*, 11664.

[50] A. R. Burns, J. S. González, H. W. Lam, *Angew. Chem. Int. Ed.* **2012**, *51*, 10827.

[51] I. –H. Chen, M. Kanai, M. Shibasaki, *Org. Lett.* **2010**, *12*, 4098.

[52] E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917.

[53] D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645.

[54] D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 5604.

[55] J. W. Rigoli, S. A. Moyer, S. D. Pearce, J. M. Schomaker, *Org. Biomol. Chem.* **2012**, *10*, 1746.

[56] A. Bonet, C. Solé, H. Gulyás, E. Fernández, *Curr. Org. Chem.* **2010**, *14*, 2531.

[57] T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 6518.

[58] C. Solé, E. Fernández, *Chem. Asian. J.* **2009**, *4*, 1790.

[59] C. Solé. A. Whiting, H. Gulyás, E. Fernández, *Adv. Synth. Catal.* **2011**, *353*, 376.

[60] D. Liu, W. Gao, C. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 1687.

[61] H. E. Sailes, J. P. Watts, A. Whiting, *J. Chem. Soc. Perkin. Trans*. **2000**, *1*, 3362.

[62] H. E. Sailes, J. P. Watts, A. Whiting, *Tetrahedron Lett.* **2000**, *41*, 2457.

[63] C. Solé, A. Tatla, J. A. Mata, A. Whiting, H. Gulyás, E. Fernández, *Chem. Eur. J.* **2011**, *17*, 14248.

[64] B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.

[65] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[66] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[67] S. Bertelsen, K. A. Jorgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[68] K. S. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253.

[69] D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196.

[70] D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, *25*, 2405.

[71] A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.* **2010**, *49*, 5130.

[72] H. Wu, S. Radomkit, J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 8277.

[73] J. A. Schiffner, K. Müther, M. Oestreich, *Angew. Chem. Int. Ed.* **2010**, *49*, 1194.

[74] A. Bonet, C. Solé, H. Gulyás, E. Fernández, *Chem. Asian. J.* **2011**, *6*, 1011.

[75] I. Ibrahem, P. Breistein, A. Córdova, *Chem. Eur. J.* **2012**, *18*, 5175.

[76] I. Ibrahem, P. Breistein, A. Córdova, *Angew. Chem. Int. Ed.* **2011**, *50*, 12036.

[77] C. J. Li, *Chem. Rev.* **2005**, *105*, 3095.

[78] S. Kobayashi, P. Xu, T. Endo, M. Ueno, T. Kitanosono, *Angew. Chem. Int. Ed.* **2012**, *51*, 12763.

[79] S. B. Thorpe, J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**, *14*, 1918.

[80] T. Kitanosono, P. Xu, S. Kobayashi, *Chem. Commun.* **2013**, *49*, 8184.

[81] T. Kitanosono, P. Xu, S. Kobayashi*, Chem. Asian. J.* **2014**, *9*, 179.

[82] M. Yamashita, *Bull. Chem. Soc. Jpn.* **2011**, *84*, 983.

[83] L. Dang, Z. Lin, T. B. Marder, *Chem. Commun* **2009**, 3987.

[84] L. Dang, Z. Lin, T. B. Marder, *Organometallics* **2007**, *26*, 2824.

[85] L. Dang, Z. Lin, T. B. Marder, *Organometallics* **2008**, *27*, 4443.

[86] B. Liu, M. Gao, L. Dang, H. Zhao, T. B. Marder, Z. Lin, *Organometallics* **2012**, *31*, 3410.

[87] J. Cid, J. J. Carbó, E. Fernández, *Chem. Eur. J.* **2012**, *18*, 12794.

[88] C. Kleeberg, A. G. Crawford, A. S. Batsanov, P. Hodgkinson, D. C. Apperly, M. S. Cheung, Z. Y. Lin, T. B. Marder, *J. Org. Chem.* **2012**, *77*, 785.

[89] J. S. Johnson, D. A. Evans, *Acc. Chem. Res*. **2000**, *33*, 325.

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

[91] D. Basavaiah, G. Veeraraghavaiah, *Chem. Soc. Rev.* **2012**, *41*, 68.

Anybody who has been

Seriously engaged in scientific work of

Any kind realizes that

Over the entrance to the gates

Of the temple of science

Are written the words:

"Ye must have faith"

(Max Planck)

2. Sequential C-B and C-F bond formation. A new approach towards vicinal difunctionalization.

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

2.1 The C-F bond

Fluoroalkyl moieties, are of a considerable importance considering the physicochemical properties that those C-F bonds have to offer to the molecule itself.

Fluorine substituents affects on physical properties relevant to compound binding, absorption and transport that can impact biological activity. Fluorine offers rather special properties in comparison to other halogens, such as high electronegativity[1], relatively small size[2,3], very low polarizability[4,5] and strong bonds. The C-F bond is one of the strongest in organic chemistry (average of 480KJ/mol), which is significantly stronger than the bonds of carbon with other halogens (average C-Cl is 320 KJ/mol) and is one of the reasons why organofluorine compounds have high termal and chemical stability.

2.2 Organofluorine compounds

Organofluorine compounds and in particular perfluorocarbons are generally very stable, chemically and physically because of the strength of the C-F bond, and the strength is even greater due to the vicinity of multiple C-F bonds, because this vicinity strengthens the skeletal C-C bonds from inductive effects[6]. The stability is so great, that generally they are only considered to be attacked by very strong reductants (Birch reduction) and very specialized organometallic complexes[7]. Concerning their application, fluorocarbons can be used as liquid dielectric. A liquid dielectric is a material in liquid state, and its main purpose is to prevent or rapidly quench electric discharges. A good liquid dielectric should have a high dielectric strength, high termal stability and chemical intertness against the construction materials used. Examples are tranformers, capacitors, high voltage cables, switch gear, etc[8].

Also, liquid breathing, which is a form of respiration in which an air-breathing organism breathes an oxygen rich liquid, can be achieved by using perfluorocarbons. The low toxicity of perfluorocarbons and their rather good capacity to dissolve gas makes them a great candidate for such studies[9]. The most promising area for the use of liquid ventilation is in the field of pediatric medicine on treatment of premature babies[10] and adults with acute respiratory distress syndrome (ARDS). Another interesting application of this fluorinated molecules, is that they can act as blood substitutors, as they can mimic or fulfill some functions of biological blood, as it is for oxygen carrier (perfluorocarbon-based oxygen carriers)[11].

Hydrofluorocarbons, organic compounds that contain fluorine and hydrogen atoms, are the most common type of organofluorine compounds. Hydrofluorocarbons can be found as

natural products, but even though fluorine is the most abundant halogen in the earth's crust, fluorine containing natural products found in nature are only thirteen, eight of which are ω-fluorinated homologues of long chain fatty acids, so formally only five natural products have been isolated excluding the fatty acids analogues[12](Figure 2.1).

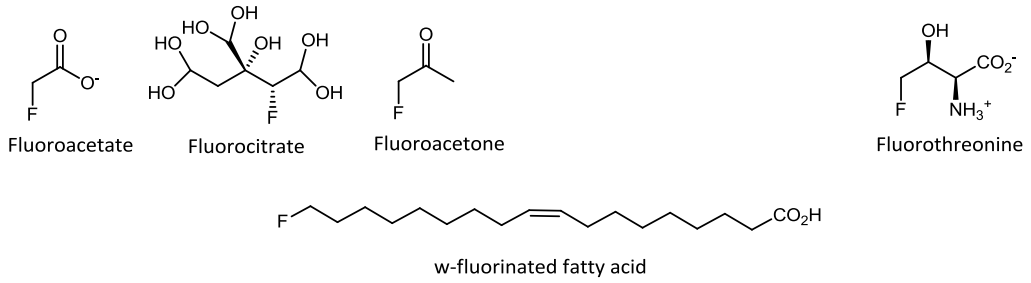


Figure 2.1. *Structure of natural products containing C-F bonds.*

Hydrfluorocarbons with few C-F bonds behave similarly to the parent hydrocarbons, but their reactivity can be altered significantly. For example, both uracil and 5-fluorouracil are colourless, high-melting crystalline solids, but the latter is a potent anti-cancer drug. The use of the C-F bond in pharmaceuticals is based on this altered reactivity[13]. Several drugs and agrochemicals contain only one fluorine center or one trifluoromethyl group. (Figure 2.2)

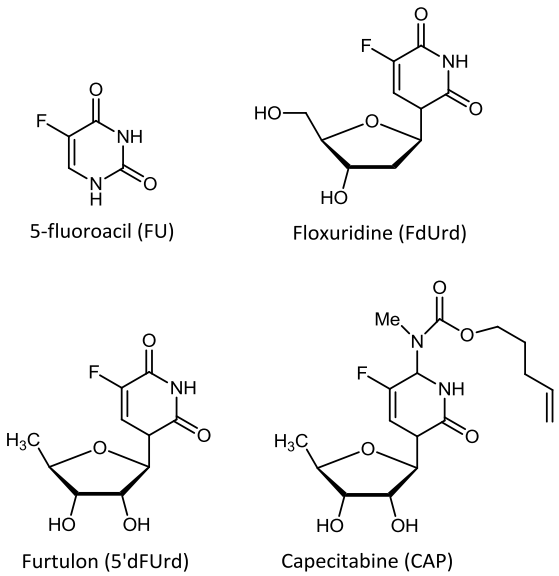


Figure 2.2. *Structure of fluorinated anti-cancer agents.*

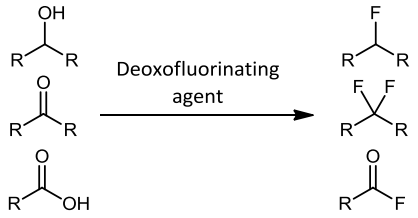
Also, to highlight the importance of fluorinated molecules, is also worth noticing that an average of 20% of pharmaceuticals and 30-40% agrochemicals contain fluorine, including 4 of the top 10 best-selling drugs[14].

The above importance of fluorinated molecules, specially hydrofluorocarbons in our case, and the fact that naturally occurring fluorinated molecules is quite rare, made scientists globally to focus their efforts towards methodologies for the synthesis of fluorinated molecules. Several methodologies can be applied, but those methodologies can be divided into four big families: Deoxofluorination (part of the nucleophilic fluorination family), nucleophilic fluorination, electrophilic fluorination, and radical fluorination.

2.3 Methodologies for preparation of C-F bonds

2.3.1 Deoxofluorination:

The deoxofluorination reaction is an effective route to introduce a fluorine atom into organic compounds. This transformation allows the direct transformation of an hydroxyl to a fluoride, a carbonyl group to a difluoromethylene, and a carboxylic acid to an acyl fluoride[15](Scheme 2.1).



Scheme 2.1. *Deoxofluorination reaction.*

Numerous reagents are able to perform the deoxofluorination reaction on all the above substrates, being the most commonly used SF_4[15], DAST (dimethylaminosulfur trifluoride)[16] and Deoxo-fluor (bis-(2-methoxyethyl)aminosulfur trifluoride[17] among others[18](Figure 2.3).

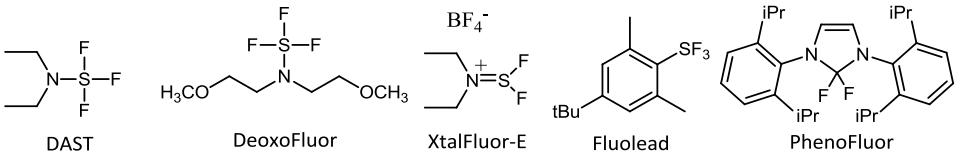
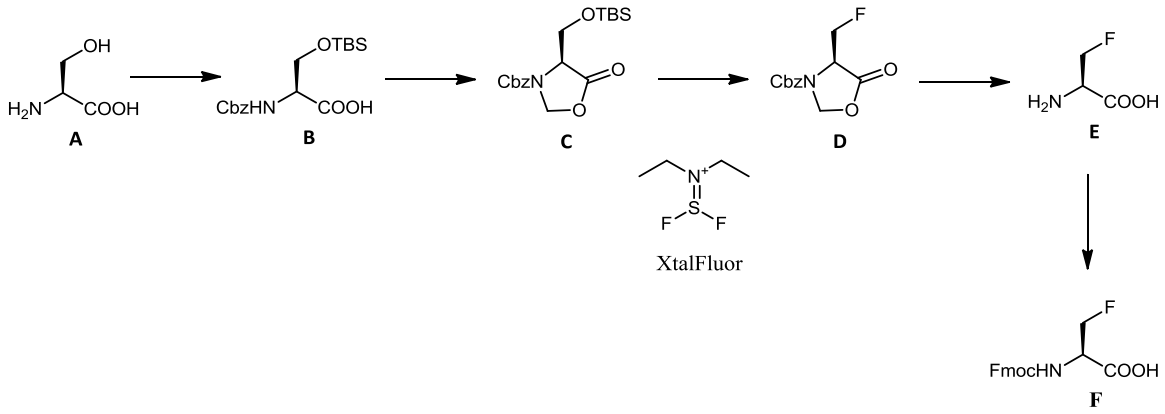


Figure 2.3. *Molecular structure of most common deoxofluorination reagents.*

Carbonyl compounds were first converted to geminal difluoromethylene functional groups with sulfur tetrafluoride[19], however, the toxicity and volatility of sulfur tetrafluoride pushed the development of other deoxomethylation reagents. The mechanism for the DAST/Deoxo-fluor is proposed to begin with a nucleophilic attack of the alcohol substrate on the sulfur atom of the reagent, to form an alkoxyaminodifluorosulfane intermediate that is activated by SN_2 attack by fluoride[20].

To exemplify the importance of this available methodology to introduce fluorine into molecules, a very recent work by Voyer et al.[21] reports an elegant synthesis of N-Fmoc protected L-Fluoroanaline, where the key step is the deoxofluorination reaction (Scheme 2.1). L-serine **A** was first protected to N-benzyloxycarbonyl-L-Serine using benzhylchloroformate, and right after the alcohol was protected as a dimethyl tert-butylsilyl ether to yield the desired protected compound **B**. Compound **B** was then treated with paraformaldehyde and catalytic amounts of p-toluenesulfonic acid in a Dean-Stark apparatus to yield oxazolidinone **C** in quantitative yield. Then, after optimized contitions, desilylation-deoxofluorination was achieved with NEt_3-3HF, XtalFluor-E in DCM to yield the desired fluorinated oxazolidinone **D** in 59% yield. Final deprotection and ring opening led to the final N-Fmoc- protected L-fluoroaniline **F** (Scheme 2.2).

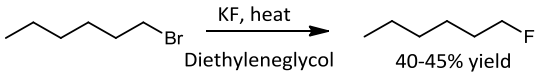
Unlike DAST and deoxofluor, fluorination with XtalFluor-type of derivatives requires the addition of amine hydrogen fluoride because after the addition of the alcohol to the Xtalfluor, the diethylamino group is fully protonated and release of fluoride does not occur. Instead of adding an external fluoride source, addition of DBU can also promote release of fluoride by deprotonation.



Scheme 2.2. *Synthesis of N-Fmoc-Fluoroaniline.*

2.3.2 Nucleophilic fluorination:

The nucleophilic fluorination reaction formally consists on the generation or utilization of "F^-" sources towards the displacement commonly of halides such as chloride and bromide. Metathesis reactions employing alkali metal fluorides are the simplest[22](Scheme 2.3).

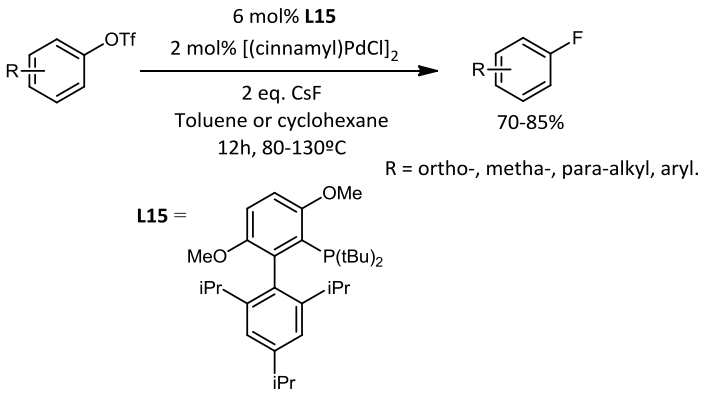


Scheme 2.3. *Synthesis of alkylfluorides from alkylhalides.*

The challenges associated with nucleophilic fluorination derive from the high electronegativity of fluorine, which contribute to high kinetic barriers to form new C-F bonds. Use of alkali metal fluoride salts is desirable due to the low cost of such reagents, even though such salts are weak nucleophiles and poorly soluble in organic solvents[23]. Crown-ethers such as 18-crown-6-ether can be used in combination with alkali metal fluorides to increase solubility of salts such as KF which often means an increase of reactivity[24]. Also, aprotic solvents specially polar aprotic solvents are preferred for nucleophilic fluorination reactions in order that the nucleophilicity of the fluoride remains unharmed by hydrogen bonding interactions[25].

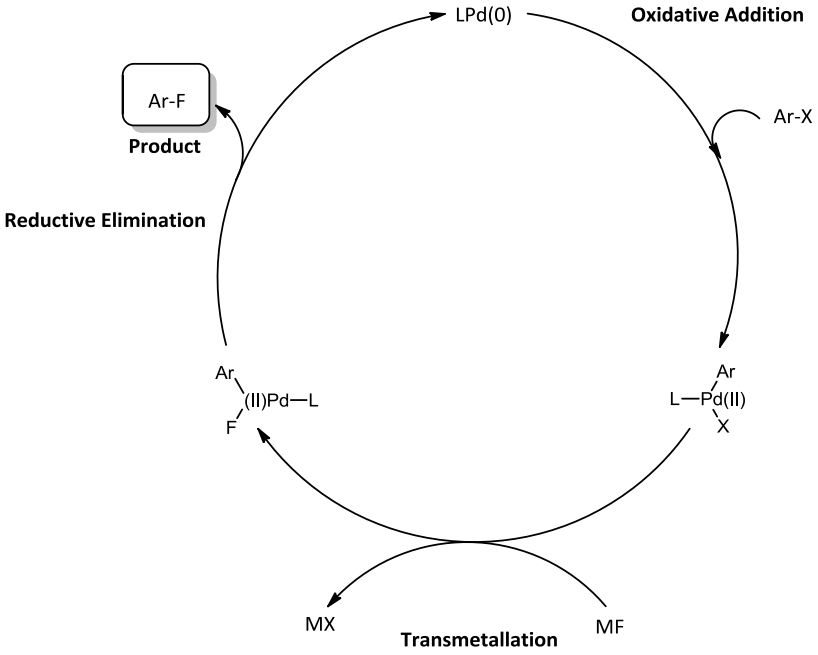
More precisely, metal-mediation/catalysis has enabled many nucleophilic fluorination reactions that are otherwise kinetically difficult to accomplish, such as the fluorination of arenes, being the first example published by Balz-Schiemman back in 1927[26]. Transition-metal promoted cross-couplings with fluorine as a nucleophile has been investigated with transition metals such as copper and palladium, among others such as ruthenium, rhodium, and platinum[27]

Concerning palladium, the first successful Pd-catalyzed cross-coupling fluorination of aryltriflates was accomplished by Buchwald et al.[28] using a bulky monodentate phosphine ligand **L15** tBuBrettPhos (Scheme 2.4) obtaining a broad substrate scope with high yields in all cases.



Scheme 2.4. *Pd-Catalyzed cross-coupling of aryl-triflates with CsF.*

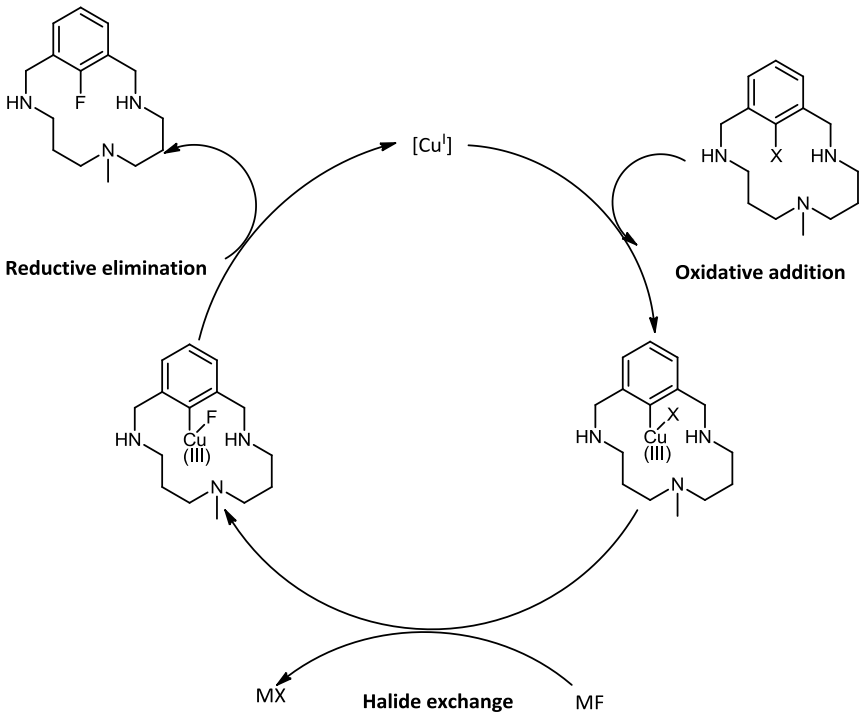
Later on by the same research group, it was proposed the plausible mechanism of the reaction, envisaging in the last step a C-F reductive elimination through a mono-nuclear, tri-coordinate palladium(II) complex took place (Scheme 2.5)[29].



Scheme 2.5. *Mechanism for the Pd-Catalyzed cross-coupling of aryl-triflates with CsF.*

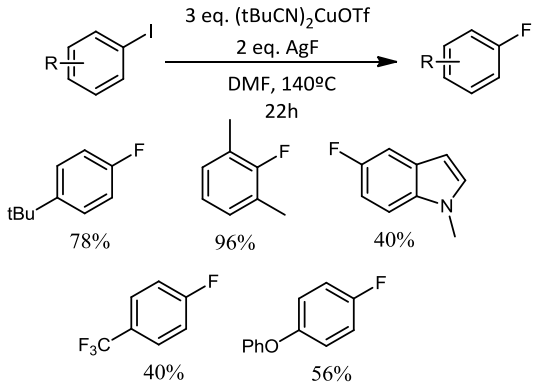
An oxidative addition-C-F-reductive elimination sequence catalyzed by copper was established by Ribas et al[30]. They proposed a catalytic cycle where upon oxidative addition, a Cu(I) complex gets oxidized to Cu(III). Oxidative addition of copper(I) into the aryl halide supported by tris(amine) ligand generates a copper (III) complex, which upon transmetallation with silver

fluoride, gives a copper(III) fluoride complex that undergoes reductive elimination to liberate the aryl fluoride product (Scheme 2.6).



Scheme 2.6. *Cu-catalyzed halide exchange on arenes with AgF.*

On the other hand, copper-mediated fluorination of electron-rich, electron-poor, as well as hindered aryl iodide substrates was reported by Hartwig et al.[31], using three equivalents of a copper(I) complex and AgF. However, the formation of hydrodehalogenated side products renders purification of the aryl fluoride products challenging (Scheme 2.7).



Scheme 2.7. *Cu-mediated fluorination of aryl iodides with AgF.*

2.3.3 Electrophilic fluorination:

Historically, most electrophilic fluorinating reagents are derived from fluorine gas, the strongest elemental oxidant known. Electrophilic fluorination reactions performed with strong oxidants such as fluorine gas, hypofluorites, fluoroxysulfates and perchloryl fluoride are challenging to perform due to the high reactivity of the reagents. Among the mentioned reagents, Xenon difluoride was developed as a more stable electrophilic fluorination source, but its high oxidation potential still limits the functional group tolerance of this reagent[32].

To overcome this problem, chemists have focused their efforts towards the synthesis of bench-stable electrophilic fluorinating reagents, being the most typical examples nowadays NFSI (N-fluorobis(phenyl)sulfonamide) **49** and F-TEDA-BF_4 (1-chloromethyl-4-fluoro-1,4-diazoniabicylo[2.2.2]octane bis(tetrafluoroborate) **50** [33] among others (Figure 2.4).

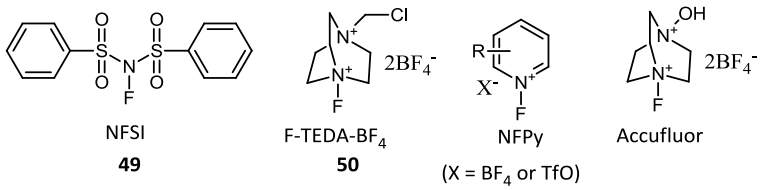
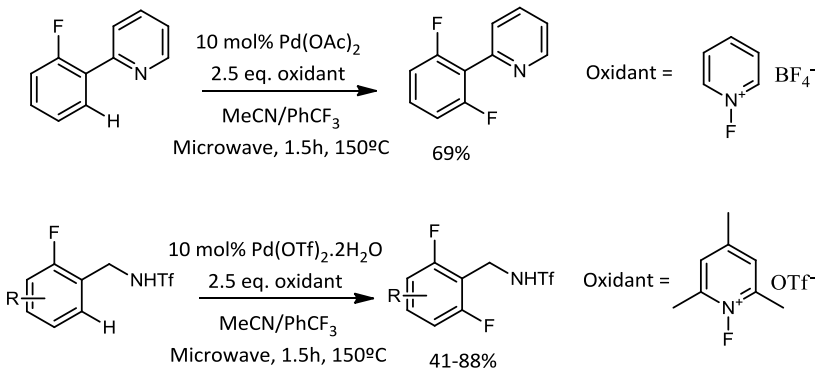


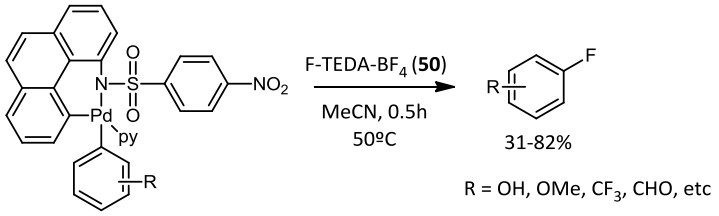
Figure 2.4. *Molecular structure of electrophilic fluorinating reagents.*

The first metal-catalyzed aromatic fluorination reactions was developed by Sanford et al.[34] by means of utilizing an ortho-coordinating group. Direct CH fluorination is desirable, but the need of coordinating groups currently limits the structural diversity of the substrates that can be fluorinated (Scheme 2.8).



Scheme 2.8. *N-directed Pd-catalyzed fluorination of arenes.*

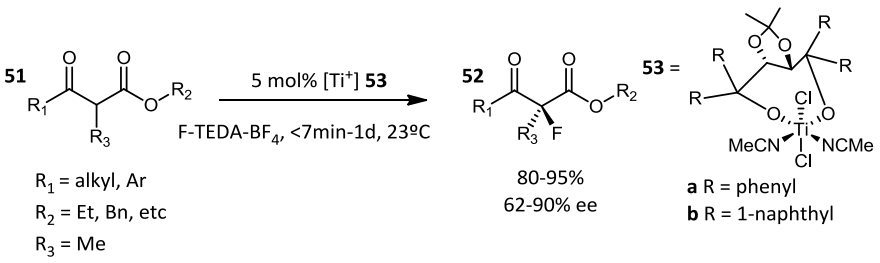
Interestingly, arylboronic acids have been used to synthesize Pd(II)benzoquinoline–sulfonamide complexes that can undergo fluorination with SelectFluor (**50**) [35], formally converting the arylboronic acid to the corresponding fluorinated compound without the need of a directing group on the aryl moiety. However, stoichiometric amounts of the Pd-complex are needed (Scheme 2.9).



Scheme 2.9. *Fluorination of Pd(II) benzoquinolyl sulfonamide complexes with F-TEDA-BF_4.*

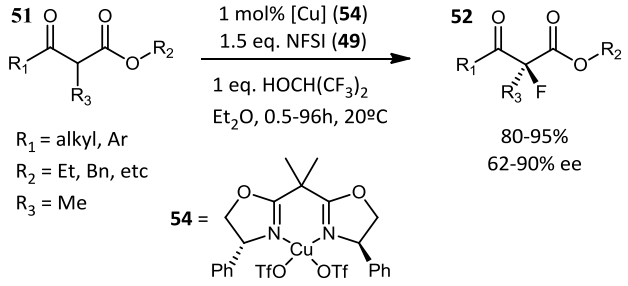
In addition to aromatic and heteroaromatic rings, alkanes can be also fluorinated by means of fluorination reaction. More paticularly, we focus in what we can call the α-fluorination of carbonyl compounds. α-fluorination of carbonyls, α'-ketocarbonyls, and related carbonyl derivatives has been achieved also by using electrophilic fluorinating reagents such as NFSI (**49**) and F-TEDA-BF_4 (**50**). Chiral versions of this transformations can also be achieved when chiral ligands are used.

For the case of dicarbonylic compounds **51**, several methods have been exploited for the two-point binding of dicarbonyl compounds to chiral Lewis acid complexes to control enantioselective fluorination. One of the first examples was reported by Togni et al.[36] reporting the enantioselective formation of α-fluoroketoesters **52** promoted by different Ti^+ complexes **53a** and **53b**. In all cases good enantioselectivities and good conversion and isolated yield values were obtained (Scheme 2.10).



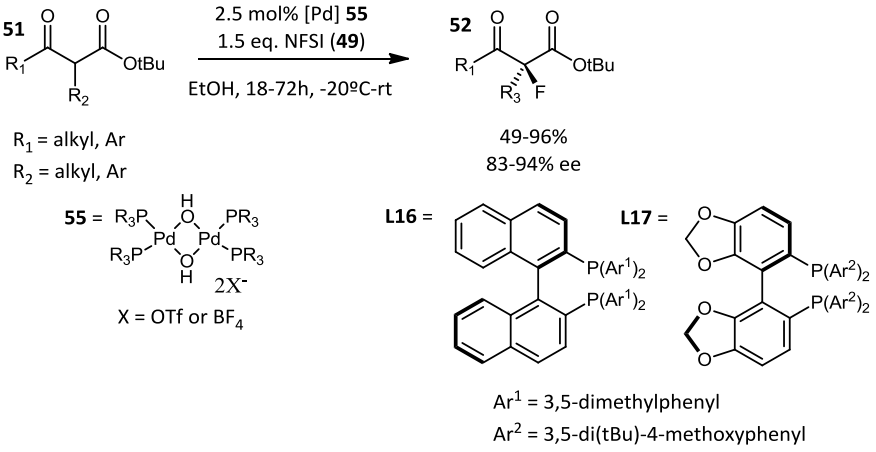
Scheme 2.10. *Ti-catalyzed asymmetric α-fluorination of β-ketoesters.*

Almost parallel to this pioneering work, Cahard et al.[37] developed a new efficient enantioselective electrophilic fluorination of both cyclic and acyclic β-ketoesters by means of chiral bis(oxazoline)-copper complexes **54**, leading to enantioenriched fluorinated compounds in high yields and good enantioselectivities (Scheme 2.11).



Scheme 2.11. *Cu-catalyzed asymmetric α-fluorination of β-ketoesters.*

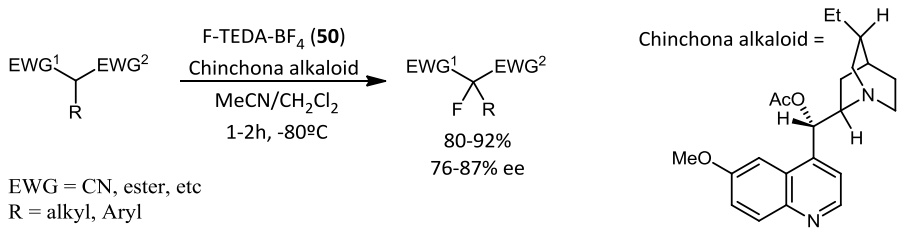
As well and almost time wise, Sodeoka et al.[38] developed another catalytic version of this transformation but instead of using Ti and Cu complexes, they used Pd-BINAP complexes. In this case, fluorination was carried out with NFSI (**49**) in ethanol in the presence of 2.5 mol% of palladium catalyst to give a record of 94% ee (Scheme 2.12).



Scheme 2.12. *Pd-catalyzed asymmetric α-fluorination of β-ketoesters.*

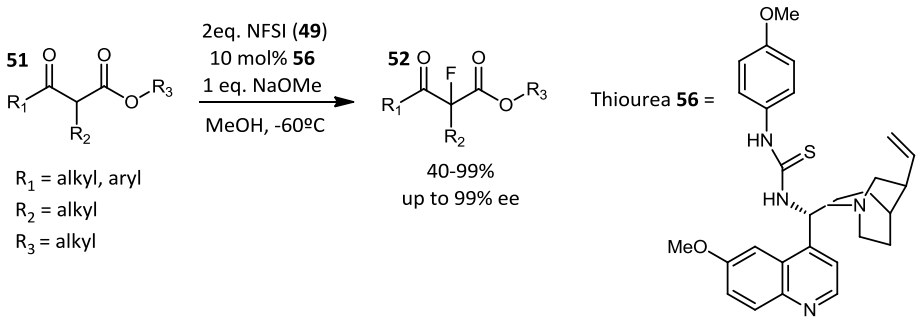
Organocatalysis is another mean by which in this case asymmetric electrophilic fluorination can be achieved, either because organocatalysts provide enantioinduction in the role of chiral

fluorinating reagents, or because reactivity with the substrate generates chiral nucleophiles. One of the first examples reported was the use of Chinchona alkaloids to enantioselectively fluorinate nucleophiles in the presence of an achiral fluorinating reagent. A pioneering work was performed by Takeuchi et al.[39] on the enantioselective fluorination of carbonyl compounds using stoichiometric amounts of chinchona alkaloids, obtaining in all cases good values of isolated yield and good enantioselectivities (Scheme 2.13).



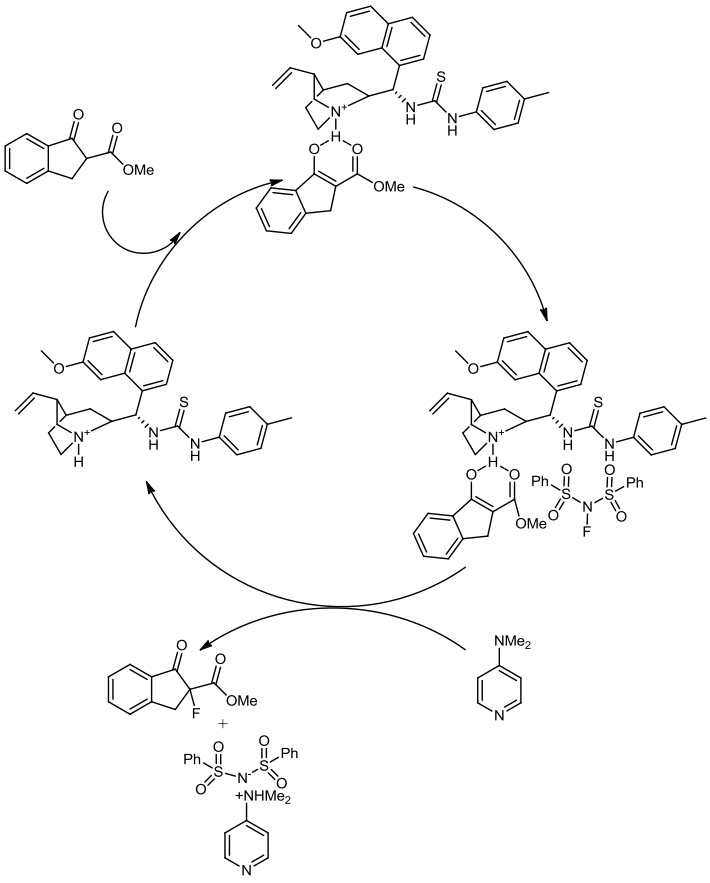
Scheme 2.13. *Enantioselective chinchona-alkaloid-mediated fluorination of C-H acidic substrates.*

Also, enantioselective α-fluorination of β-ketoesters can be accomplished using chinchona-alkaloid-derived thiourea catalysts as reported by Niu et al.[40]. Obtaining after optimized conditions, high values of conversion, isolated yield and enantioselectivity (Scheme 2.14).



Scheme 2.14. *Enantioselective thiourea chinchona-alkaloid-mediated fluorination of C-H acidic substrates.*

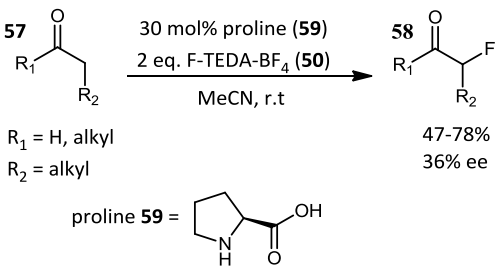
Mechanistically it is proposed that the thiourea plays a role similar to the previously mentioned chinchona alkaloids, coordinating to the carbonylic group to generate an enolate on the α-position capable to react with the electrophilic fluorine source. However in this example, the thiourea group favours coordination with NFSI (**49**) via hydrogen bond, and the 1,3-dicarbonyl group interacts with the tertiary amine group (Scheme 2.15).



Scheme 2.15. *Proposed mechanism for the enantioselective thiourea chinchona-alkaloid mediated fluorination of C-H acidic substrates.*

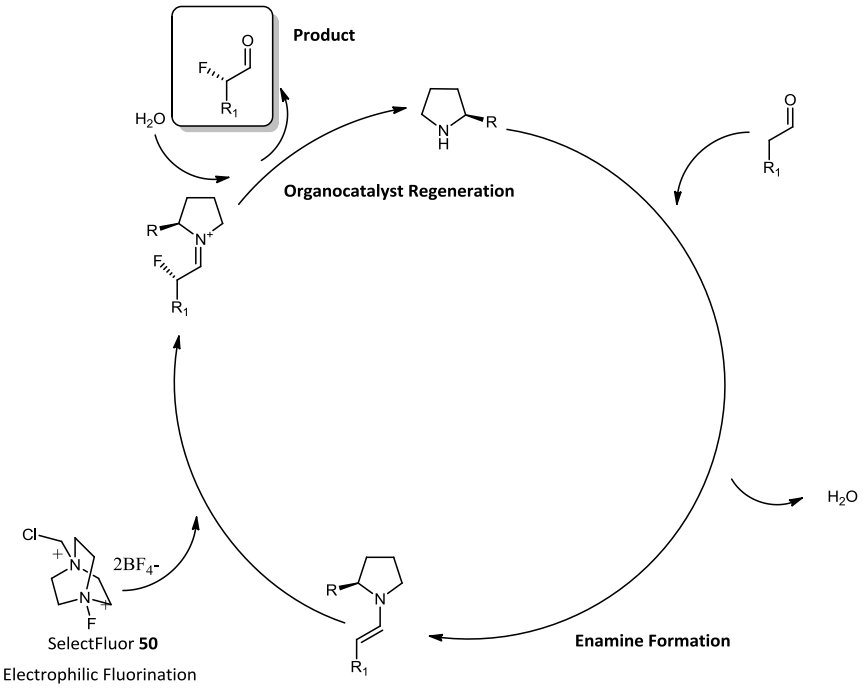
Still in the organocatalytic framework, enamine catalysis has been investigated towards the obtention of α-fluorinated carbonyl compounds. Enantioselective organocatalytic α-fluorination of aldehydes and ketones has been achieved in 2005 by Enders[41], MacMillan[42], Jorgensen[43] and Barbas[44] almost timewise.

Enders and coworkers were the first to report the enantioselective α-fluorination of aldehydes and ketones **57** using different chiral secondary amines as catalysts and Selectfluor (**50**) as the electrophilic fluorinating reagent. However the results were poor in terms of yield and enantioselectivity (Scheme 2.16)



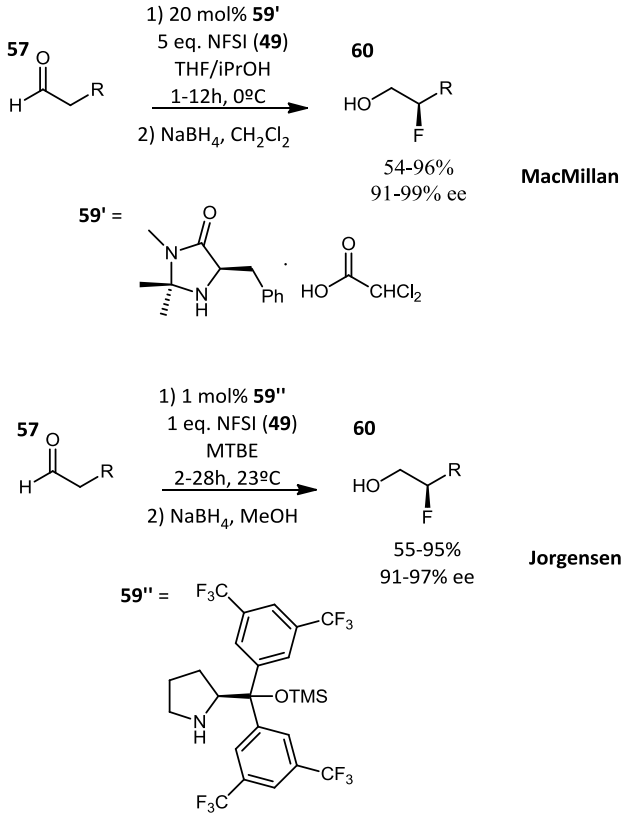
Scheme 2.16. *Proline-catalyzed enantioselective α-fluorination of aldehydes and ketones.*

Mechanistically, the secondary amine coordinates to the carbonylic group to form an enamine, which is nucleophilic on the alpha position. The nucleophile is then capable to react with the electrophilic fluorinating reagent. Once the substitution on the α-carbon has taken place, the secondary amine is recovered and can coordinate to another molecule of substrate to continue the catalytic cycle (Scheme 2.17).



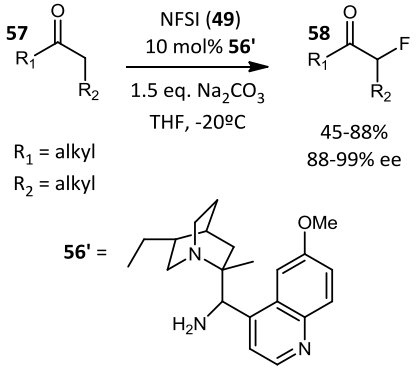
Scheme 2.17. *Proposed catalytic cycle for enamine-catalyzed α-fluorination of carbonilic compounds.*

The aldehyde α-fluorination method described by MacMillan[42] demonstrates a broader substrate scope, while the method described by Jorgensen[43] utilizes lower catalyst loadings and electrophilic fluorinating reagent. Both cases provided good conversions and enantioselectivities for the substrates used (Scheme 2.18).



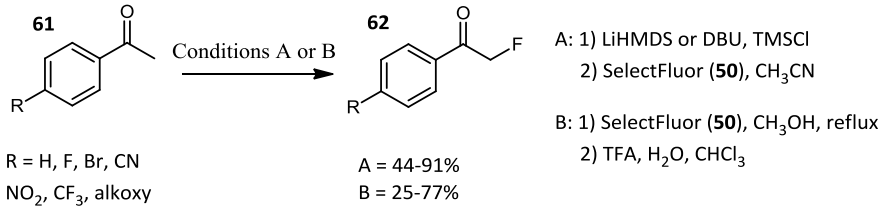
Scheme 2.18. *Organocatalytic asymmetric α-fluorination of aldehydes.*

Similar work consisting on the α-fluorination of ketones has been performed also by MacMillan in the field of enamine catalysis[45]. They had overcome the problem of enamine catalysis for ketones **57**, that was the slow enamine formation and obtantion of different rotational isomers. The optimal system used was a primary amine functionalized chinchona alkaloid, that enables α-fluorination of a broad variety of carbo- and heterocyclic substrates, obtaining in all cases good values of isolated yield and excellent enantioselection (Scheme 2.19).



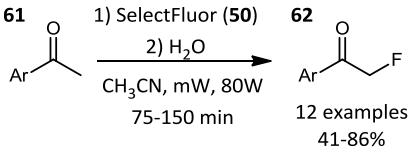
Scheme 2.19. *Organocatalytic enantioselective α-fluorination with primary amine functionalized chinchona alkaloid.*

Also, a recent breakthrough on fluorine chemistry led to the formation of the corresponding α-fluoroketones. Stavber et al.[46] reported a solvent-free methodology for the electrophilic fluorination of fluorindanones using NFSI (**49**) or SelectFluor (**50**). Yields are reported to be good to excellent, even though the substrate scope is limited. Also, Hoff et al.[47] reported two electrophilic pathways to produce 1-arylethanones (Scheme 2.20). The first one (Conditions A), implied the formation of a trimethylsilyl enol ether followed by an electrophilic fluorination with Selectfluor (**50**), whereas the second method (Conditions B) was the direct electrophilic fluorination of the ketone followed by the cleavage of the corresponding fluorinated dimethyl acetals formed during the reaction. Both conditions gave the monofluorinated acetophenone derivatives in moderate to good yields.



Scheme 2.20. *Synthesis of 1-arylethanones.*

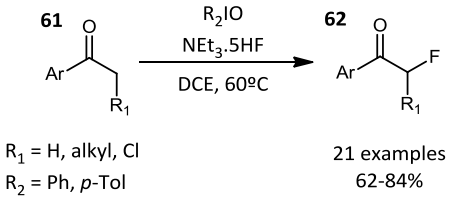
The same year, Stavber et al.[48] reported the direct electrophilic fluorination of a variety of ketones **61** in an aqueous miscellar system yielding α-fluorinated cyclic and acyclic ketones in moderate to excellent yield (Scheme 2.21).



Scheme 2.21. *α-fluorination in aqueous miscellar system.*

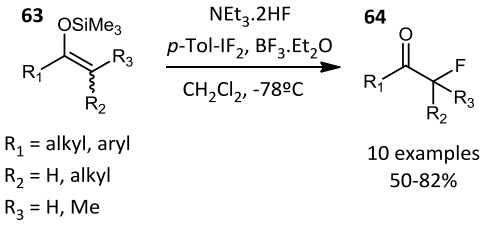
Recently, in terms of α-fluorination of carbonylic compounds, not only electrophilic fluorinating reagents such as NFSI (**49)** and F-TEDA-BF_4 (**50**) and their analogues have been used, other reagents of different nature have been proven to fluorinate selectively under the right conditions. Kitamura et al.[49] reported the direct monofluorination of ketones using iodosylarenes and NEt_3.5HF in excess. The desired α-monofluorinated compounds were

obtained in good yields. However, the scope of the reaction was limited to acetophenone derivatives (Scheme 2.22).



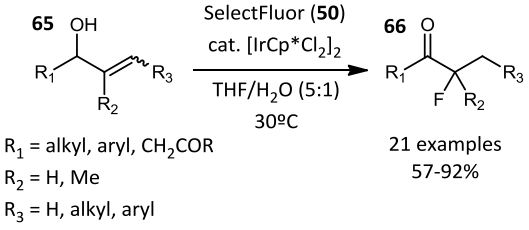
Scheme 2.22. *α-fluorination using iodosylarenes.*

Hypervalent iodine-based reagents demonstrated to be useful for the formation of α-fluorinated ketones starting from silylated enol ethers. Hara et al.[50] reported the use of *p*-Tol-IF_2 for the fluorination of cyclic and acyclic silyl enol ethers in moderate to good yields (Scheme 2.23).



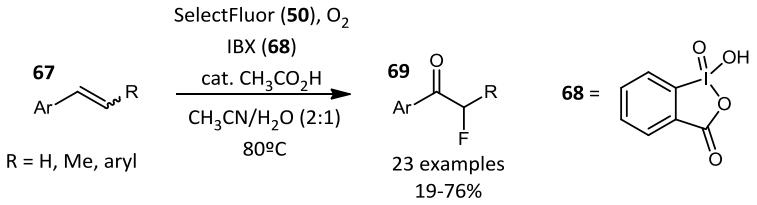
Scheme 2.23. *α-fluorination of silylated enol ethers.*

Also, fluorination of allylic alcohols is another mean by which in the end, an α-fluoroketone can be obtained. Martín-Matute et al.[51] developed an iridium-catalyzed formation of α-fluoroketones starting from allylic alcohols. They obtained α-fluorinated ketones derivatives in good yields using a low catalyst loading of the iridium complex (1 mol%). Interestingly, those conditions also allowed the regioselective formation of α'-fluoro-β-dicarbonyl compounds (Scheme 2.24).



Scheme 2.24. *Ir-catalyzed fluorination of allylic alcohols.*

In 2014, Yang et al.[52] reported the metal-free oxyfluorination of styrene derivatives **67** for the synthesis of α-fluorinated ketones (Scheme 2.25). The metal-free conditions allowed the formation of a variety of α-fluorinated aryl- and heteroaryl ketones in moderate to good yields.

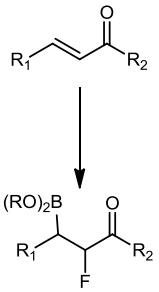


Scheme 2.25. *Oxofluorination of syterene derivatives.*

Not only carbonylic compounds (ketones, aldehydes and β-ketoesters) have been successfully α-fluorinated in the past years, other electronwithdrawing groups have been also successfully fluorinated on the alpha position, such as imines[53], amides[54], nitriles[55], nitro compounds[56], phosphonates[57], sulfones[58] and β-ketoamides[59].

2.4 Objectives of work

In basis to the specified properties of fluorinated compounds, we became interested to perform a difunctionalization of α,β-unsaturated carbonyl compounds with vicinal C-B and C-F bonds.



The specific objectives are:

-Search for metal and metal-free methodologies that would allow us the obtention of α-fluorinated β-borylated carbonyl compounds.

-Compare the advantages and limitations for each methodology explored.

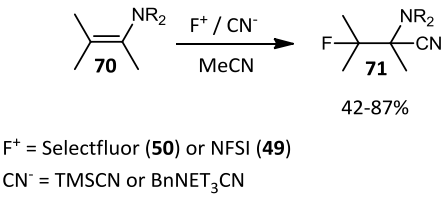
-Extend the substrate scope to stablish a general methodology.

-The diaestereo- and enantioselective issues.

The obtention of such compounds will be interesting, because to the best of our knowledge, there are no examples in the literature concerning electrophilic fluorination-nucleophilic boron addition to α,β-unsaturated carbonyl compounds. The obtained compounds, beyond the fact that they will be new in the literature, would offer tremendous scientific potential as difunctionalized compounds.

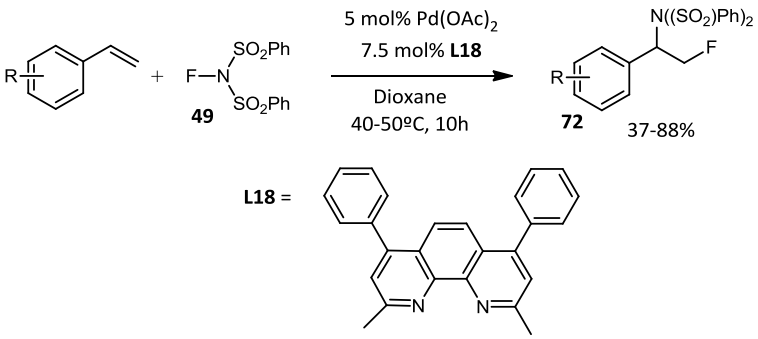
2.5 Results and discussion

We were aware that electrophilic fluorination combined with nucleophilic addition across unsaturated carbon-carbon bonds are complex reactions. The fluorination-cyanation of functionalized alkenes **70**, such as enamines, can be performed sequentially without metal catalyst[60]. The fluorocyanation is hypothesized to occur via electrophilic fluorination of the enamine, followed by trapping of the iminium intermediate with cyanide. In all cases, good to excellent isolated yields were obtained (Scheme 2.26) despite the fact that diaestereomeric ratios were low.



Scheme 2.26. *Fluorocyanation of enamines.*

The intermolecular aminofluorination of vinylarenes, involves a reactivity where the fluorinating reagent NFSI (**49**) functions not only as the fluorinating reagent but also as an aminating reagent. The reaction afforded vicinal fluoroamine products with very high regioselectivity. As the authors suggest[61], the transformation involves fluoropalladation of vinylarenes as a key step for the C-F bond formation (Scheme 2.27).

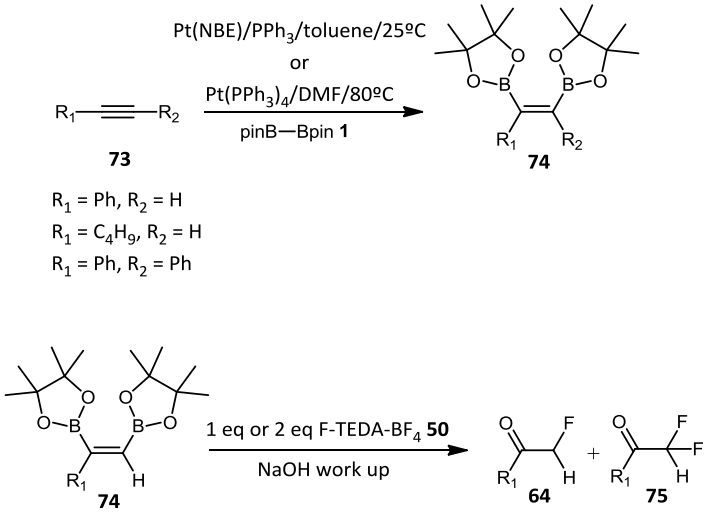


Scheme 2.27. *Intermolecular aminofluorination of styrenes with NFSI (**49**).*

To the best of our knowledge, there are no examples in the literature concerning electrophilic fluorination-nucleophilic borylation to α,β-unsaturated carbonyl compounds. However, there

are a couple methodologies concerning boron and fluorine chemistry addition on alkynes, both of which are previously reported by our research group.

In 2005, Fernández et al.[62] reported the synthesis of α-fluorinated and α,α-difluorinated carbonyl compounds from alkynes through α-fluoro-deboration process. The novelty of the process relies on the fact that two new functional groups (carbonyl and fluorine) are regioselectively formed through an organoboron intermediate (Scheme 2.28). The authors first performed a diboration of terminal alkynes with B_2pin_2 (**1**) using Pt(0) complexes to achieve and isolate cis-1,2-bis(boryl)alkenes. The addition of Selectlfuor (**50**) to the diborated intermediate **74** and NaOH to quench the reaction led to the electrophilic fluorination on the terminal position and the oxidation of the internal Bpin unit to the corresponding carbonyl compound, with a mixture close to 50/50 α-fluorination and α,α-difluorination using 1 eq of **50**, but almost complete selectivity to the α,α-difluorination product when using 2 eq. of **50**.

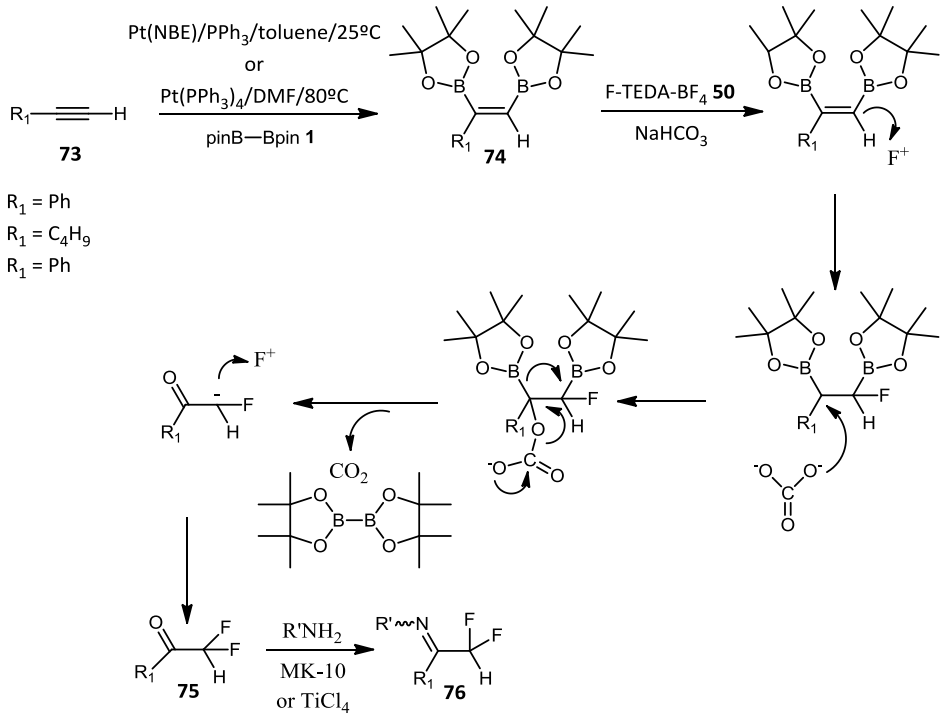


Scheme 2.28. *Diboration of alkynes followed by fluorodeboronation.*

A couple years later, also Fernández et al.[63] gave more insight into the previously described methodology and they were capable to synthesize, in one-pot, α,α-difluorimines from alkynes with a catalytic tandem diboration/fluorination/imination reaction.

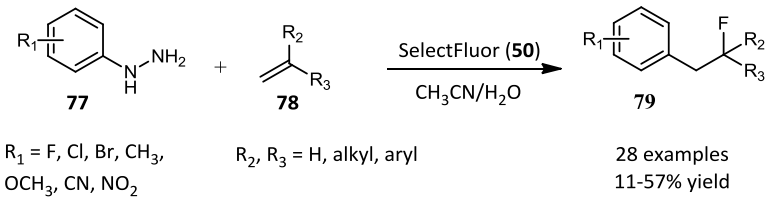
Mechanistically, once the diboration product has been formed through Pt-catalysis, it is postulated that the N-F reagents could interact with the alkenyl diboronate ester intermediates through an electrophilic attack. They postulated a concerted mechanism, where an electrophilic attack of F^+ takes place at the most electronegative C-B bond in the

alkenyldiboronate esters, followed by nucleophilic attack of the carbonate base, ultimately leading to the formation of carbon dioxide, the regeneration of B_2pin_2 (**1**) with concomitant formation of the second C-F bond at the terminal postion. Finally, the imination proceeds easily in the same reaction vessel upon addition of the corresponding amine and dehydrating agent (Scheme 2.29).



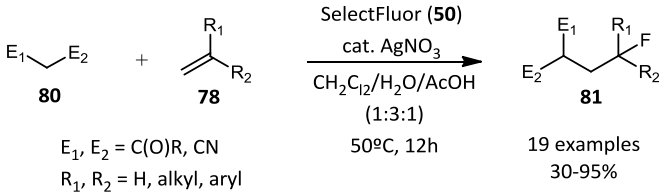
Scheme 2.29. *Mechanism for tandem diborylation/fluorination/imination of alkynes.*

In 2014, a pioneering work concerning the carbofluorination of alkenes was reported by Kindt and Heinrich et al.[64]. SelectFluor (**50**) acted as an oxidant to generate aryl radicals, and also acted as a fluorine source in the final radical fluorination step. Low to moderate yields were obtained (Scheme 2.30).



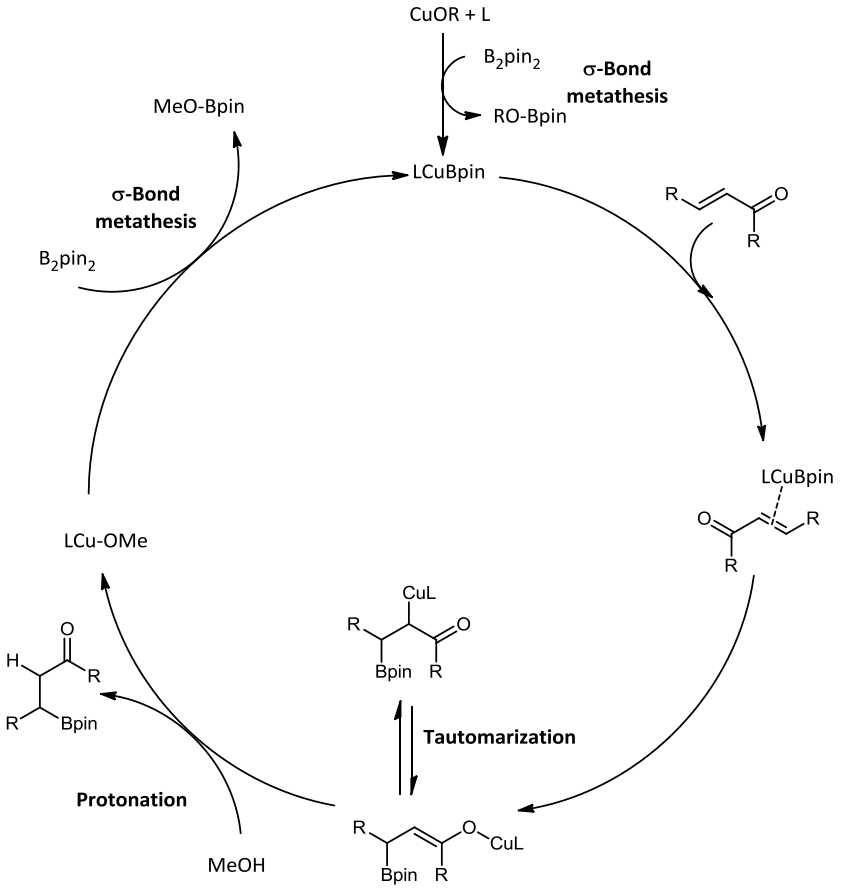
Scheme 2.30. *Carbofluorination of alkenes.*

Also in 2014, Li et al.[65] described a silver-catalyzed carbofluorination of unactivated alkenes with active methylene compounds and acetone (Scheme 2.31). These reactions are perfomed under mild conditions and allowed the carbofluorination of a wide range of substrates in good yields.



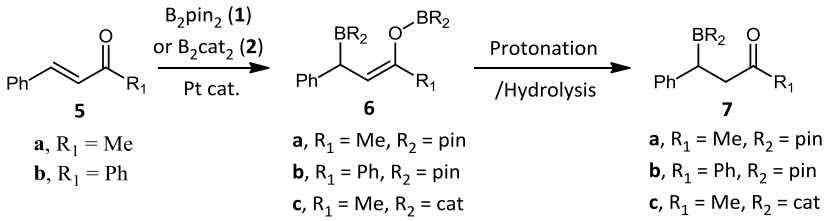
Scheme 2.31. *Carbofluorination of alkenes.*

At that point, we envisaged an electrophilic fluorination of an enolate formed in the β-boration of α,β-unsaturated carbonyl compounds. However, in those typical reaction conditions we need methanol, which is the key additive for the protonation of this enolate to yield the final product, but also for the regeneration of the Cu-OR. (Scheme 2.32).



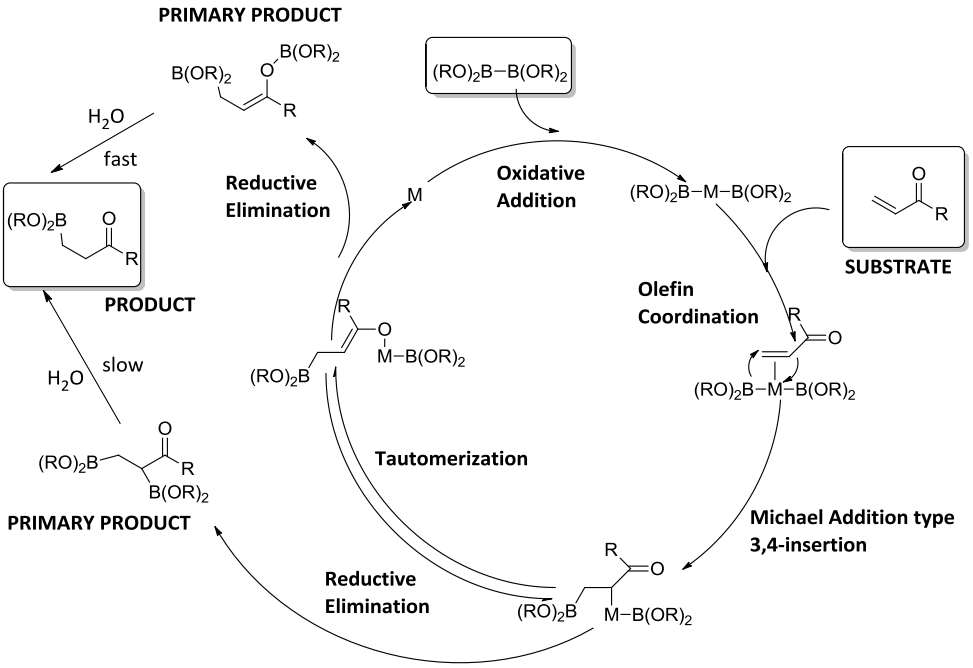
Scheme 2.32. *Proposed catalytic cycle for the Cu-mediated β-boration of α,β-unsaturated carbonyl compounds.*

We screened methodologies where the borylation of α,β-unsaturated substrates can be performed without the use of any protic solvent in the reaction media, to avoid the protonation of the enolate, in our case. We realized that the first β-boration reactions of activated alkenes, carried out by Marder and co-workers[64], proceed in the absence of protic additive. The researchers studied the reaction of the diboron reagents B_2pin_2 (**1**) and B_2cat_2 (**2**) with α,β-unsaturated ketones in the presence of a Pt(0) catalyst. Changing the structure of the tetraalkoxydiboranes did not alter the chemo- nor regioselectivity of the reactions, obtaining the 1,4-diborated derivatives as the only primary products. These intermediates, as expected, were sensitive to exposure to water, and readily formed the β-borated derivatives by hydrolysis (Scheme 2.33).



Scheme 2.33. *Pt-catalyzed β-boration of electron-deficient olefins.*

For the formation of the 1,4-diborated product, the migratory insertion of the C=C double bond should be followed by tautomerization, leading to the coordinated enol intermediate before the reductive elimination step. Whether tautomerization occurs before reductive elimination or not, apparently depends on the structure of the substrate. In the case of esters, the tautomerization might be unfavorable because of the energy difference between acids, esters and their corresponding ethane-1,1-diol tautomers and the corresponding aldehydes, ketones and their enol tautomers[67]. The ester moiety unit is thermodynamically more stable than ketones and aldehydes, therefore tautomerization is unfavored (Scheme 2.34)



Scheme 2.34. *Plausible mechanism for the Pt-catalyzed β-boration of electron-deficient olefins.*

In that context, we considered using Pt to promote a 1,4-diborated intermediate from our α,β-unsaturated carbonyl substrates, and then instead of performing aqueous work-up to favor the protonolysis, we would add electrophilic fluorinating reagents in order to promote the electrophilic trapping of fluorine. We initiated this preliminary study using cyclohexenone **38** as model substrate.

We selected the appropriate solvent that could be equally effective for β-boration and fluorination reactions (Table 2.1). DMF was not efficient to conduct the 1,4-diboration, whereas toluene, CH_3CN and THF favored the conjugate B addition, but not the fluorination. In that context, we selected toluene as the solvent of choice and we performed the reaction sequence starting by the borylation with toluene and after solvent evaporation, the fluorination with DMF. Under those new reaction conditions, organofluoroborane compounds **83** and **84** could be obtained by extension of the fluorination reaction time (Table 2.1, entries 5-6).

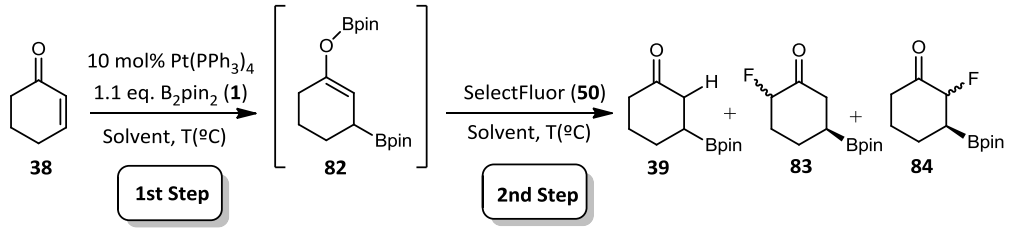
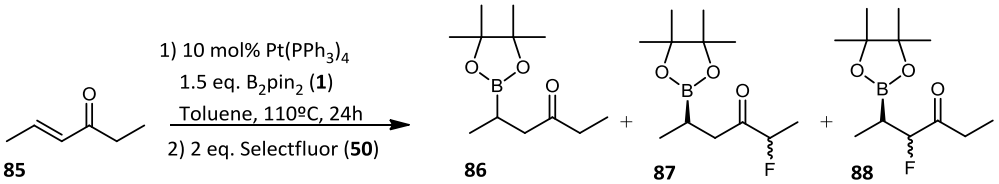


Table 2.1. *Pt-catalyzed β-boration/α-fluorination of 2-cyclohexen-3-one (**38**).*

Entry	1st Step Solvent/T(ºC)	2nd Step Solvent/T(ºC)	Conv(%)[d]	39(%)[d]	83(%)[d]	84(%)[d]
1[a]	Toluene/110	Toluene/30	75	100	--	--
2[a]	CH_3CN/110	CH_3CN/30	71	100	--	--
3[a]	THF/60	THF/30	50	100	--	--
4[a]	DMF/100	DMF/30	<10	100	--	--
5[a,b]	Toluene/110	DMF/30	81	78	20	2
6[b,c]	Toluene/110	DMF/30	65	52	30	18

[a]Standard conditions: $Pt(PPh_3)_4$ (0.02mmol) and B_2pin_2 (**1**) (0.27 mmol), Solvent (2 mL), cyclohexenone **38** (0.25 mmol), 110ºC , 24 hours. After 24 hours the reaction was cooled down to 30ºC before addition of F-TEDA-BF_4 (**50**) (0.5 mmol), rt, 24.[b]Same as but replacing solvent. [c]Fluorination step perfomed for 72h.[d]Conversion and selectivity calculated using ^{1}H NMR spectroscopy and G.C analysis.

We extended the Pt-catalyzed sequential polifunctionalization to the non-cyclic α,β-unsaturated substrates. 4-Hexene-3-one (**85**) was selected as the model substrate, obtaining the following results (Scheme 2.35).

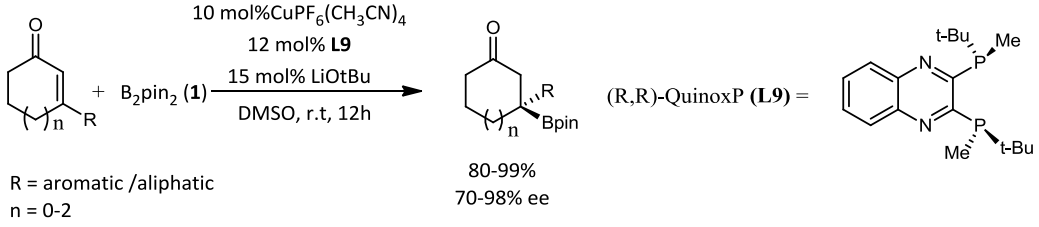


Solvent: DMF, 30ºC, 24h	80%	15%	5%	Conversion = 87%
Solvent : DMF, 30ºC, 72h	46%	39%	15%	Conversion = 97%

Scheme 2.35. *Pt-catalyzed β-borylation/α-fluorination of 4-hexene-3-one (**85**).*

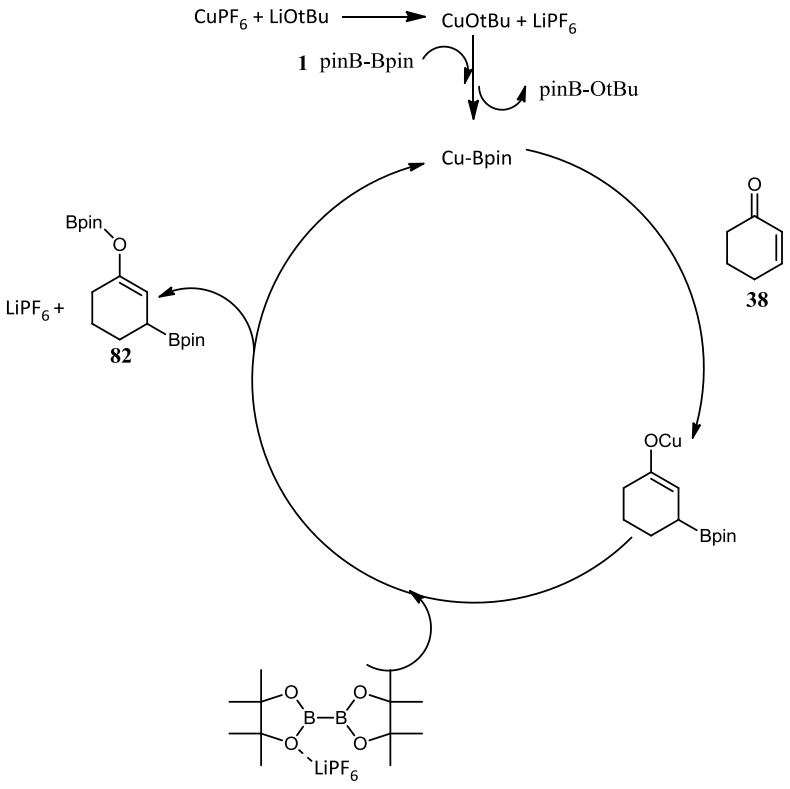
From the previous results it can be said that the Pt-catalyzed borylation/fluorination reaction was more conveninent for the 4-hexene-3-one (**85**) used as substrate, but still not satisfactory. In all cases, still considerable amounts of protonation took place, and when the fluorination worked to certain extent, a mixture of regioisomers was obtained, therefore we considered that the Pt-catalyzed wasn't a good approach towards the synthesis of our desired α-fluorinated β-borylated carbonyl compounds in a selective way. Besides, Pt is a quite expensive metal and nowadays several other metals/methodologies can be applied instead.

We found that Shibasaki and coworkers[68], developed a catalytic asymmetric synthesis of chiral tertiary organoboronic esters through conjugate boration of β-substituted cyclic enones, with $CuPF_6(CH_3CN)_4$ in the absence of any protic source. To obtain higher yields, a lithium alkoxide needs to be used (Scheme 2.36). Lithium salts have also been assumed to accelerate reaction rates in Cu-catalyzed asymmetric allylcyanide additions[69].



Scheme 2.36. *Synthesis of chiral tertiary organoboronic esters from β-substituted cyclic enones.*

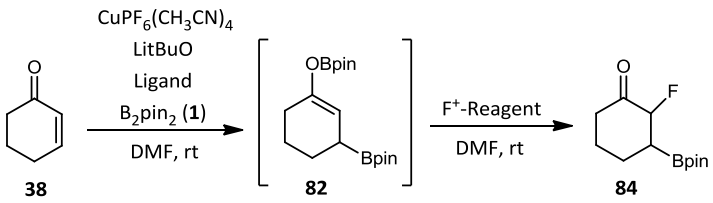
A catalytic cycle involving the possible role of the in-situ generated $LiPF_6$ was proposed. Reaction between $CuPF_6$ and LiOtBu generates CuOtBu and $LiPF_6$. Then, the active species Cu-Bpin, formed through transmetallation with B_2pin_2 (**1**), performs a conjugate addition to the enone to afford a C-enolate stabilized by copper. $LiPF_6$ might accelerate the turnover limiting step (which is the regeneration of the nucleophile Cu-Bpin[69]) by enhancing the electrophilicity of B_2pin_2 (**1**) acting as a Lewis acid, to afford finally the 1,4-diborated intermediate **82**, which upon aqueous work-up, protonates to generate the β-boryl cycloenone (Scheme 2.37).



Scheme 2.37. *Proposed catalytic cycle including the role of* $LiPF_6$.

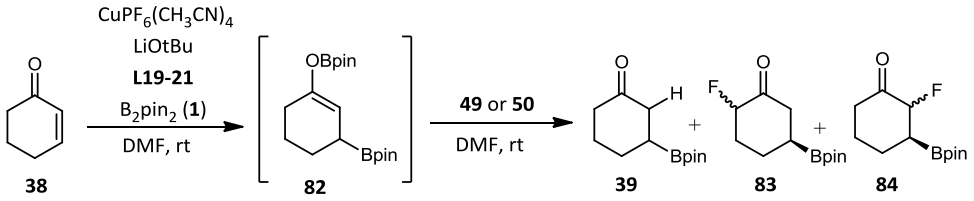
The authors also postulate another working hypothesis for the origin of acceleration effects of $LiPF_6$. In an alternative catalytic cycle the reaction of Cu-enolate with $LiPF_6$ would generate a transient Li enolate. The Li enolate should be more reactive towards transmetallation with boron, and the reaction of the Li enolate with tBuO-Bpin generates the 1,4-diborated product **82** and LiOtBu. The catalytically active CuOtBu is regenerated by the reaction between LiOtBu and $CuPF_6$.

We looked at this protocol with enthusiasm, since DMF and DMSO were used as polar aprotic solvents with success. We envisaged the formation of the 1,4-diborated intermediate, and "quench" the reaction with an electrophile such as F-TEDA-BF_4 (**50**) or NFSI (**49**), to finally obtain the α-fluorinated β-borylated carbonyl compound (Scheme 2.38).



Scheme 2.38. *Sequential borylation/fluorination of* α,β*-unsaturated carbonyl compounds.*

This experimental setting provided results concerning the obtention of organofluoroborane compounds, as it is shown in the following table (Table 2.2).



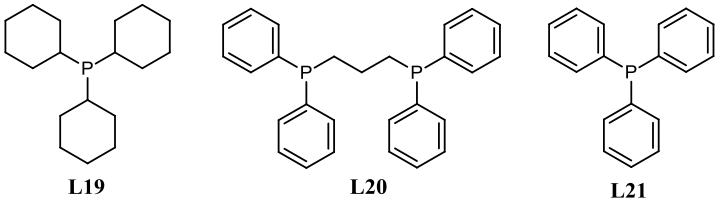


Table 2.2. *Sequential borylation/fluorination of cyclohexenone **38**.*

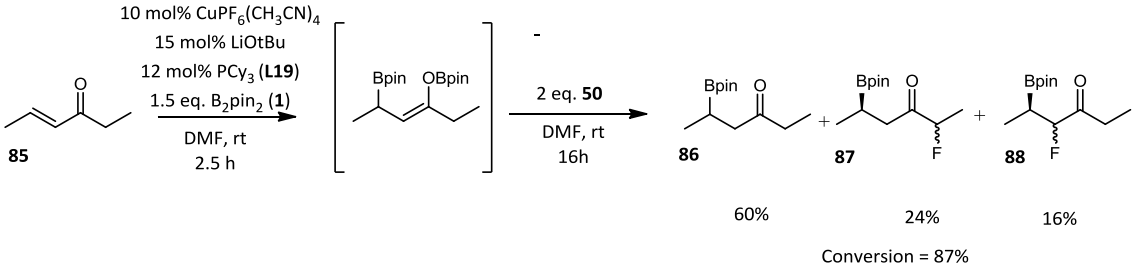
Entry	Ligand(%)	Conv(%)[e]	39(%)[e]	83(%)[e]	84(%)[e]
1[a]	**L19**(12)	77	41	58	traces
2[a]	**L20**(12)	56	83	16	traces
3[a]	**L21**(12)	80	72	29	traces
4[b]	**L19**(12)	65	66	33	traces
5[c]	**L19**(12)	86	50	49	traces
6[d]	**L19**(12)	75	75	--	--

[a]Standard conditions: $CuPF_6$ (0.025mmol), B_2pin_2 (**1**) (1.5 eq.), LiOtBu (0.015 mmol), Ligand **L19**-**L21** (0.03 mmol), DMF (2 mL), cyclohexenone **38** (0.25 mmol), rt, 16h. After 16h, addition of the fluorinating reagent **50** (0.5 mmol) rt, 24 hours.[b]B_2pin_2 (**1**) (1.1 eq.). [c]Selectfluor (**50**) (3 eq.). [d]NFSI (**49**) (2 eq.) [e]Conversion and selectivity determined by ^{1}HNMR spectroscopy and GC analysis.

Three different phosphine ligands were screened (**L19**-**L21**) to determine their influence on the reaction. PPh_3 (**L21**) (12 mol%) was the most convenient to modify $CuPF_6(CH_3CN)_4$, since 80% conversion of substrate was observed, despite the fact that the major product was the β-borylated-protonated **39**. PCy_3 (**L19**) (12 mol%) was more convenient to promote the borylated fluorinated product **83**. The desired product with vicinal C-B and C-F bonds was formed in very small amounts.

Taking into consideration that the α-protonated-β-borated ketone product was the main organoboron derivative, we postulated that a higher amount of fluorinating reagent (SelectFluor **50**) would benefit the second step, however the fluorination was not completed (Table 2.2, entry 5). The replacement of SelectFluor (**50**) by NFSI (**49**), allowed the formation of the α-protonated-β-borated product without fluorination (Table 2.2, entry 6)

We extended the catalytic sequential polifunctionalization to non-cyclic α,β-unsaturated substrates. 4-Hexen-3-one (**85**) was selected as the model substrate and converted up to 87%. Under optimized conditions, the α'-F, β-Bpin carbonyl compound **87** was obtained in 24% and α-F, β-Bpin ketone **88** in 16% (Scheme 2.39).



Scheme 2.39. *Sequential borylation/fluorination of 4-hexen-3-one (**85**).*

We became interested to limit the period of time for the β-boration to diminish the protonolosys of the enones.

When we carried out the copper catalyzed β-boration reaction of **85** (150 minutes), followed by the addition of 2 eq. F-TEDA-BF_4 (**50**) (16h), we observed quantitative formation of the regioisomer **88** (Table 2.3, entry 1), in which C-F was formed vicinal to the C-B bond. Substrate **85** was completely transformed and only a small percentage of non-fluorinated β-borated ketone was observed (Table 2.3, entry 1). In this particular case, the diaestereoisomer *anti* was preferentially formed versus the *syn* diaestereomer (77/23 dr). The major *anti* isomer was characterized by comparison with the reported analogue α-fluoro β-amino esters synthesized using a similar methodology of conjugate addition of lithium amides to α,β-unsaturated esters and sequential electrophilic fluorination[70]. Even though the results were good on the first attempt, we wanted to optimize conditions and know if subtle modifications would alter the reaction towards the regioselective obtantion of α-fluoro β-boryl ketones. The summarized results are shown in Table 2.3.

Interestingly, changing the conditions for the one-pot system was detrimental towards the reaction outcome. Increasing the amount of Cu precursor and base (Table 2.3 entries 2 and 3) led to significantly lower selectivity towards the desired fluoroborated compound. Changing the base from LiOtBu to NaOtBu also led to disappointing results concerning chemoselectivity (Table 2.3 entry 4). Also, the lack of phosphine, or changing to electrophilic fluorinating reagent from SelectFluor (**50**) to NFSI (**49**), led to complete formation of the β-borated

compound **86**, and only traces of the desired product could be observed (Table 2.3 entries 5 and 6).

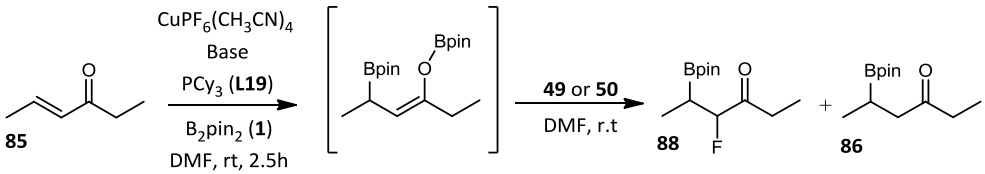


Table 2.3. *One pot borylation/fluorination of 4-hexen-3-one (**85**).*

Entry	$CuPF_6$ (%)	PR_3(%)	Base(%)	F^+-source	Conv(%)[b]	88(%)[b] (*syn*/*anti*)	86[b] (%)
1[a]	10	PCy_3 (12)	LiOtBu (15)	SelectF (2 eq.)	99	94 (23/77)	6
2[a]	20	PCy_3 (12)	LiOtBu (15)	SelectF (2 eq.)	99	16 (27/73)	84
3[a]	10	PCy_3 (12)	LiOtBu (30)	SelectF (2 eq.)	85	52 (23/77)	48
4[a]	10	PCy_3 (12)	NaOtBu (15)	SelectF (2 eq.)	85	13 (23/77)	87
5[a]	10	---	LiOtBu (15)	SelectF (2 eq.)	99	--	100
6[a]	10	PCy_3 (12)	LiOtBu (15)	NFSI (2 eq.)	99	4	96

[a]Standard conditions: $CuPF_6$ (0.025mmol), B_2pin_2 (**1**) (1.5 eq.), LiOtBu (0.025 mmol), PCy_3 (**L19**) (0.03 mmol), DMF (2 mL), α,β-unsaturated ketone **85** (0.25 mmol), rt, 2.5h. After 2.5h, addition of the fluorinating reagent **49** or **50** (0.5 mmol) rt, 16 hours. [b]Conversion and selectivity determined by ^{1}HNMR spectroscopy and GC analysis.

With the optimized conditions in hand, we proceed to settle the substrate scope to stablish the extension of this methodology (Table 2.4). In general the Cβ-boron bond can be quantitatively formed from the conjugate B addition in all the substrates studied and the efficiency of the fluorination step as well as the diaestereomeric ratio (dr) seem to be dependent on the nature of the substrate. Terminal substrate **89** could be totally borylated with B_2pin_2 (**1**) within 2 hours, and subsequent fluorination led to the α-fluoro β-(pinacol)boryl ketone **95** with a conversion of 87% as a single isomer. When the long chain aliphatic ketones 5-methyl 2-hepten-4-one **90** and 3-hepten-2-one **91** were subjected to the sequential β-boration / α-fluorination, the substrates were converted into the desired products **96** and **97** up to 72-75%, with identical dr (78/22) in favor to the *trans* isomer. The more hindered substrate 1-phenyl-3-buten-2-one **92** was quantitatively converted into the corresponding α-fluoro β-boryl ketone **98** but with a slight increase of the diaestereoselectivity (80/20). Formation of substituted cyclohexanone **100** led to the best results in terms of chemoselection and diaestereomeric ratio in favor of the *anti* isomer (90/10)(Table 4 entry 8).

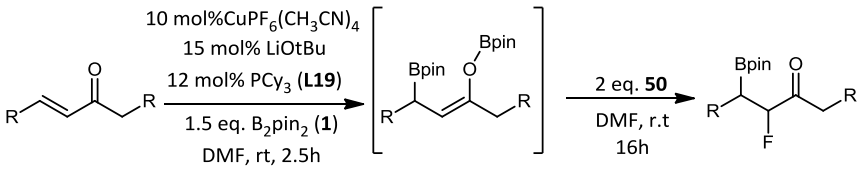
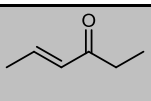
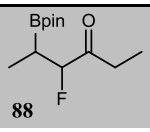
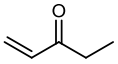
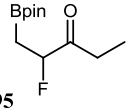
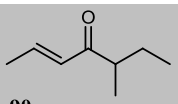
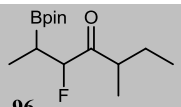
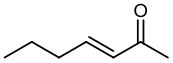
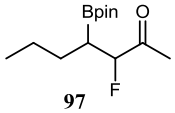
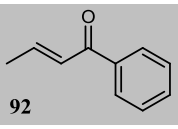
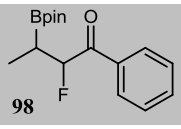
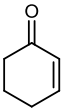
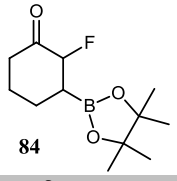
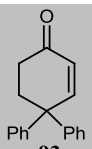
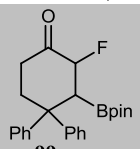
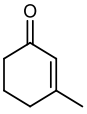
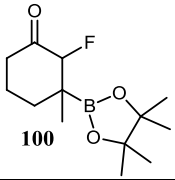


Table 2.4. *Scope of α-fluoro β-boryl ketones from α,β-unsaturated ketones.*

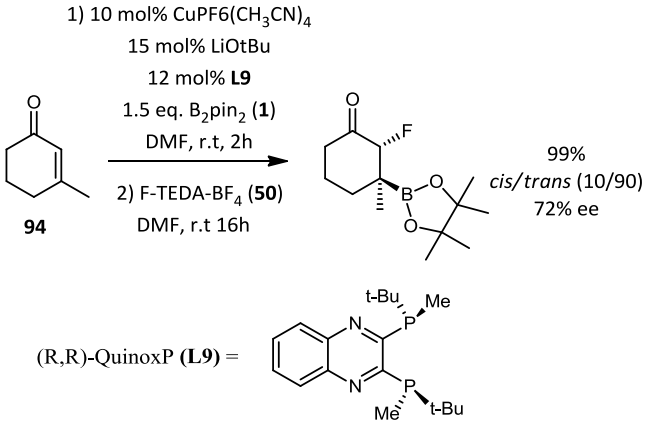
Entry	Substrate	Product	Conv(%)[b]	I.Y.(%)	(*cis*/*trans*)[b] or (*syn*/*anti*)[b]
1[a]	 **85**	 **88**	94	30	(23/77)
2[a]	 **89**	 **95**	87	--	--
3[a]	 **90**	 **96**	75	60	(22/78)
4[a]	 **91**	 **97**	72	--	(22/78)
5[a]	 **92**	 **98**	99	17	(20/80)
6[a]	 **38**	 **84**	99	20	(33/67)
7[a]	 **93**	 **99**	99	90	(40/60)
8[a]	 **94**	 **100**	99	87	(10/90)

[a]Standard conditions: $CuPF_6$ (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.03 mmol), DMF (2 mL), α,β-unsaturated ketone (0.25 mmol), rt, 2.5h. After 2.5h, addition of the fluorinating reagent **50** (0.5 mmol) rt, 16 hours. [b]Conversion and selectivity determined by ^{1}HNMR spectroscopy and GC analysis.

It is interesting to note that, to the best of our knowledge, there is only one precedent in the literature in which the corresponding boron enolate from 3-substituted 2-cyclohexen-1-one,

reacted further with benzaldehyde as an electrophilic reagent to generate the corresponding aldol product with (6.5/1) dr[68]. In that precedent, the enantioselective conjugate boration using $CuPF_6(CH_3CN)_4$ modified with the chiral ligand (R,R)-QuinoxP* (**L9**), provided the tetrasubstituted carbon with high level of enantioselectivity (>90% ee). With this elegant precedent in mind, we decided to perform the copper catalyzed conjugate boration in an asymmetric way to further react the boron enolate with F-TEDA-BF_4 (**50**).

Substrate 3-methyl 2-cyclohexen-1-one (**94**) was borylated with $CuPF_6(CH_3CN)_4$ and (R,R)-QuinoxP (**L9**), and further addition of the electrophilic fluorine source, led to the corresponding α-fluorinated β-borylated cyclic enone with comparable values of conversion and *cis*/*trans* diaestereoselection. The enantioselectivity was 72%, slightly lower than the borylated protonated compound (Scheme 2.40). This synthetic approach represents an alternative to the current efforts to develop enantioselective aliphatic fluorination routes.



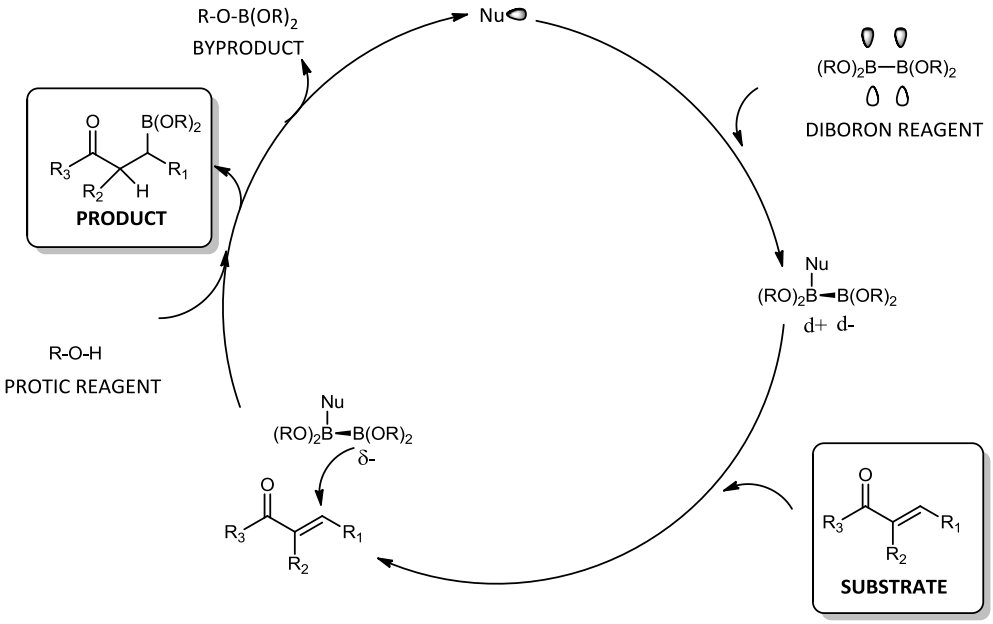
Scheme 2.40. *Enantioselective one-pot borylation/fluorination sequence.*

At that point of the research, in which we have explored a metal catalyzed methodology in order to obtain our desired compounds, we also wanted to test if in a metal free context, the fluorination/borylation of ketones can be possible.

Metal-free borylation is a concept that has emerged in the last few years. Hoveyda and co-workers have observed that N-heterocyclic carbenes could promote conjugate 1,4-addition of B_2pin_2 (**1**) to cyclic enones, in the presence of base, at room temperature[71]. Shortly after, Fernández and coworkers demonstrated that the reaction could also be carried out in the presence of base, MeOH and tertiary phosphorous compounds as additives, although slightly higher temperatures (max.70ºC) were required to reach full conversions. Several α,β-unsaturated esters, acyclic and cyclic ketones could be β-borated with this novel catalytic

system. Interestingly, the application of chiral phosphines favored that the products could be obtained in up to 95% enantiomeric excesses[72].

Complete understanding of the mechanism of the organocatalytic β-boration reactions is one of the recent challenges in the chemistry of organoboranes. According to our current view, in these metal free systems, the diboron reagents are simply activated by carbenes and bases. The quaternization polarizes the B-B bond, and initiates the nucleophilic attack of the sp^2 boryl unit at the β-carbon of the substrate (Scheme 2.41).



Scheme 2.41. *Organocatalytic β-boration of α,β-unsaturated carbonyl compounds.*

The nucleophilic attack of the sp^2-boryl unit to the β-position, would formally generate an enolate, that in MeOH is rapidly protonated to form the product of β-boration. We envisaged however, that if we used stoichiometric amounts of base to activate the diboron source, and a system absent of MeOH, this enolate formed organocatalytically might survive long enough to react with an electrophile present in the media, in that case F^+.

In order to generate the enolate in the most stable form possible, we screened conditions using LiOtBu, since lithium is known to have strong oxophilicity and therefore might coordinate to the oxygen of the enolate in order to generate stabilization, and the $^-$OtBu would be the nucleophile that will activate the diboron reagent. The conditions screened are summarized in Table 2.5.

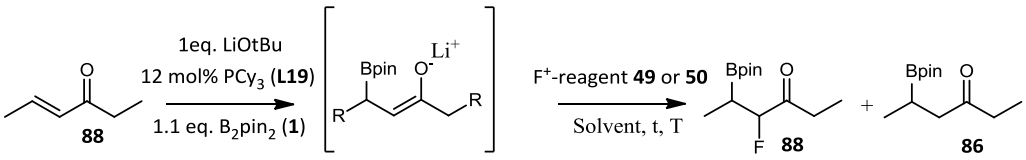


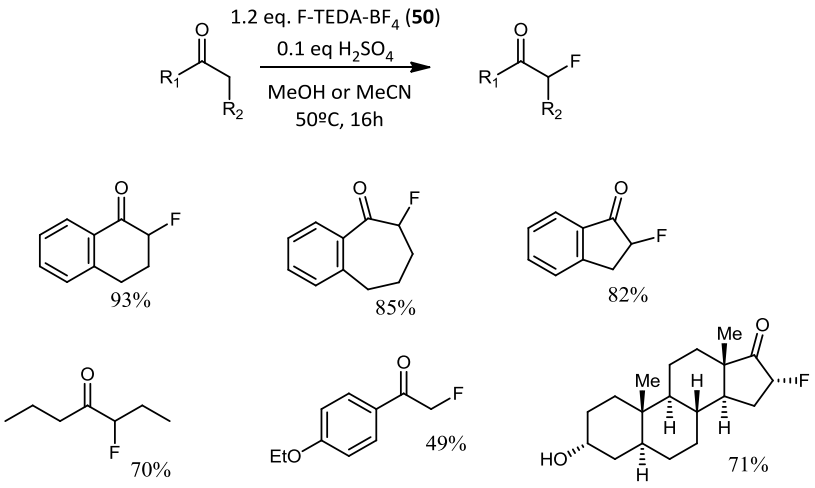
Table 2.5. *Metal-free approach to synthesize of α-fluoro β-boryl compounds.*

Entry	F^+-source	Solvent	Temp.	Time	Conv(%)[b]	88(%)[b]	86(%)[b]
1[a]	SelectFluor(**50**) (2eq)	THF	20ºC	16h	99	--	>99
2[a]	SelectFluor(**50**) (2eq)	Toluene	20ºC	16h	99	--	>99
3[a]	SelectFluor(**50**) (2eq)	DCM	20ºC	16h	86	--	>99
4[a]	SelectFluor(**50**) (2eq)	DMF	20ºC	16h	80	--	>99
5[a]	SelectFluor(**50**) (2eq)	DMSO	20ºC	16h	80	--	>99
6[a]	SelectFluor(**50**) (2eq)	THF	-78ºC	3h	5	--	>99
7[a]	NFSI (**49**) (2eq)	THF	-78ºC	3h	5	--	>99

[a] *Standard conditions:* Dry solvent (2 mL) ,PCy_3 (**L19**) (0.025 mmol), LiOtBu (0.25 mmol) and B_2pin_2 (**1**) (0.275 mmol), substrate **88** (0.25 mmol), and the whole mixture was left stirring for 5 more minutes. Finally, fluorinating reagent (0.375 mmol) was added to the whole mixture for the corresponding time at the corresponding temperature. [b] Conversion and selectivity determined by ^{1}HNMR spectroscopy and GC analysis.

The solvents employed such as THF, Toluene and DCM, didn't lead to any formation towards the desired product (Table 2.5 entries 1-3). DMF which worked perfectly on the previous methodology, in that case it didn't give any desired product, just as DMSO (Table 2.5 entries 4-5). Also lowering the temperature down to -78ºC and using NFSI (**49**), which is a methodology applied for the conjugate addition of lithium amides to α,β-unsaturated esters to obtain α-fluoro β-amino esters[54], didn't work either, and the substrate was barely converted to products.

At that point, we turned our attention to an alternative fluorination protocol via in situ formation of a nucleophilic enol intermediate under acidic conditions. The efficiency of this direct electrophilic fluorination of ketones has recently been demonstrated by Batey et al.[73]. The reactions are generally quite selective leading to the formation of monofluorinated products (Scheme 2.42).



Scheme 2.42. *α-fluoroketones synthesized by direct fluorination with H_2SO_4.*

Since this reaction has been reported to proceed most efficiently in MeOH, we found a principle of compatibility with the organocatalytic β-boration carried out in MeOH as solvent. Therefore, we performed an organocatalytic β-boration of α,β-unsaturated ketones followed by the addition of 1 eq. of F-TEDA-BF_4 (**50**) and 10 mol% of H_2SO_4. Upon this attempt, we obtained transformation of ketone **85** into the corresponding α'-fluoro β-boryl compound **87** with a conversion of 29% (Table 2.6 entry 1). The need for an excess of fluorination reagent was justified by the higher conversion observed on **87** when 2 eq. of F-TEDA-BF_4 (**50**) were used (Table 2.6, entry 2).

To highlight the efficiency of the one pot methodology we performed a parallel study in which 2 eq. of F-TEDA-BF_4 (**50**) were added to an isolated β-borated ketone **86**. Under identical conditions, the electrophilic fluorination reaction transformed **86** into **87** with slightly higher conversion (Table 2.6, entry 3). The amount of sulfuric acid was optimized at 10% because greater amounts of the acid catalyst did not significantly improve the yield (Table 2.6 entries 4 and 5), and lower amounts decreased the reaction outcome (Table 2.6 entry 6). The application of other acid catalysts such as HNO_3, HCOOH and CF_3COOH were less efficient in this direct electrophilic fluorination. Alternative fluorinating reagents such as NFSI (**49**) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate were inefficient under optimized reaction conditions.

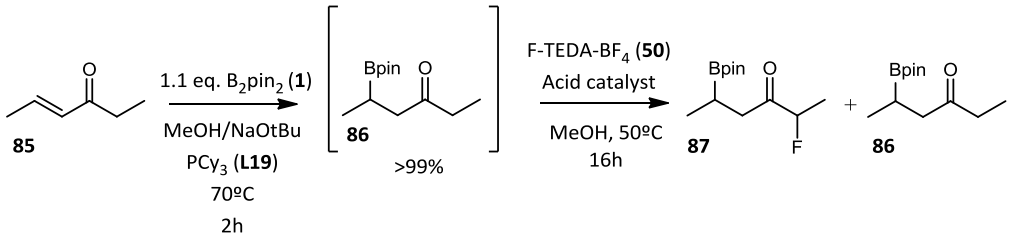
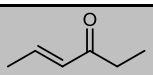
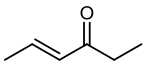
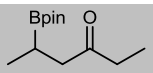
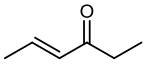
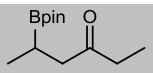
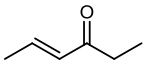
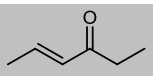


Table 2.6. *One-pot organocatalytic nucleophilic β-boration /electrophilic α-fluorination of 4-hexen-3-one (**85**).*

Entry	Subtstrate	Catalyst	Conv(%)[c]	87(%)[c]	I.Y.(%)	86(%)[c]
1[a]	 **85**	H_2SO_4 (10 mol%)	99	29		71
2[b]	 **85**	H_2SO_4 (10 mol%)	99	63	60	36
3[a]	 **86**	H_2SO_4 (10 mol%)	99	84	74	16
4[a]	 **85**	H_2SO_4 (20 mol%)	99	71	67	29
5[a]	 **86**	H_2SO_4 (20 mol%)	99	86	75	14
6[a]	 **85**	H_2SO_4 (5 mol%)	99	33		66
7[a]	 **85**	HNO_3 (10 mol%)	99	16		84

[a]*Standard conditions for organocatalytic* β*-boration*: substrate **85** (0.25 mmol), B_2pin_2 (**1**) (1.1 eq.), PCy_3 (**L19**) (10 mol%), NaOtBu (5 mol%), MeOH (2 mL), 70ºC, 2h. *Standard conditions for electrophilic fluorination:* Selectfluor (**50**) (0.25 or 0.5 mmol), H_2SO_4 95% (10 mol%,0.025mmol), 50ºC, 15h.[b]F-TEDA-BF_4 (**50**) (0.25 mmol).[c]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

This new methodology of sequential Cβ-B and Cα'-F bond formation was also extended to the use of other diboron reagents. When bis(neopentylglycolato)diboron (B_2neop_2) (**3**) or bis(hexyleneglycolato)diboron (B_2hex_2) (**4**) were used instead of B_2pin_2 (**1**), substrate **85** was quantitatively β-borated and consecutive electrophilic fluorination led to the formation of the corresponding α'-fluoro β-boryl ketones **101** and **102**, respectively (Table 2.7, entries 2 and 3). It should be pointed out that the one-pot synthesis of α'-fluoro β-boryl ketones **87**, **101** and

102 were carried out with total regioselectivity but as a 1:1 mixture of diaestereomers. The substrate scope involved other α,β-unsaturated ketones.

The regioselective α'-electrophilic fluorination of the β-borated ketones seems to be controlled by the more thermodynamically stable enol intermediate[57].

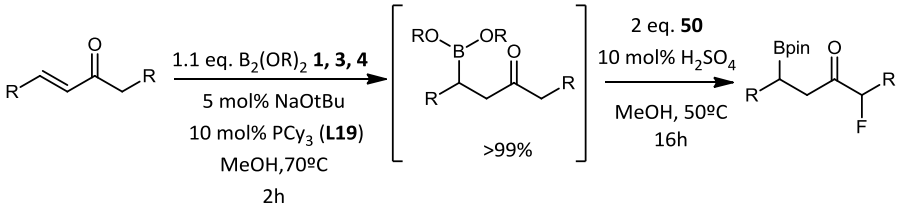
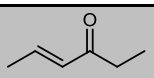
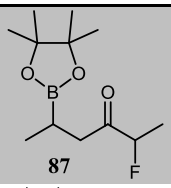
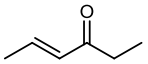
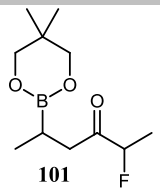
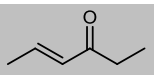
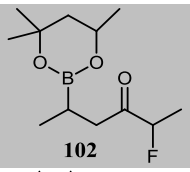
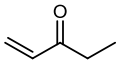
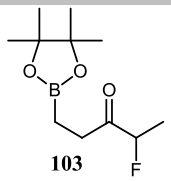
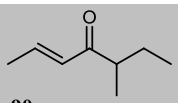
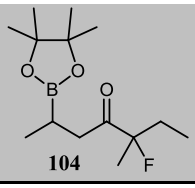


Table 2.7. *Scope of α'-fluoro β-boryl ketones from α,β-unsaturated ketones.*

Entry	Substrate	Product	Conv(%)[b]	I.Y.(%)
1[a]	 85	 87	84	74
2[a]	 85	 101	70	61
3[a]	 85	 102	73	--
4[a]	 89	 103	68	--
5[a]	 90	 104	56	51

[a]*Standard conditions for organocatalytic* β-*boration*: substrate (0.25 mmol), $B_2(OR)_2$ **1**, **2** or **3** (1.1 eq.), PCy_3 (**L19**) (10 mol%), NaOtBu (5 mol%), MeOH (2 mL), 70ºC, 2h. Selectfluor (**50**) (0.5 mmol), H_2SO_4 95% (10 mol%,0.025mmol), 50ºC, 15h. [b]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

The substrate scope involved α,β-unsaturated ketones such as 1-penten-3-one (**89**) and 5-methyl-2-hepten-4-one (**90**). The terminal substrate **89** was quantitatively borylated with B_2pin_2 (**1**) and subsequent fluorination led to the α'fluoro β-(pinacol)boryl ketone **103** with

conversion up to 68%. The most hindered substrate **90** was efficiently β-borated and the electrophilic fluorination also took place regioselectively at the substituted Cα' but with lower conversion to yield product **104**.

2.6 Conclusions

In this chapter we have screened and developed methodologies towards the difunctionalization of α,β-unsaturated carbonyl compounds, involving fluorine and boron chemistry.

A key aspect towards the synthesis of the mentioned compounds was the enol/enolate stability in the catalytic cycle in order to react with a F^+ source once the borylation has taken place.

Concerning the metal-catalyzed approach, we have seen that a desired protocol to obtain the α-fluoro β-boryl ketones consist on using a very specific type of copper precursor ($CuPF_6(CH_3CN)_4$ and base (LiOtBu) in a polar aprotic solvent such as DMF. The induction time for the formation of the 1,4-diborated product was crucial; longer times than 2h led in the end to a mixture of fluorinated-borylated regioisomers.

In all the cases studied, the conversion, chemo- and regioselectivity were moderate to high. It is worth to note that diaestereoselection was substrate dependent, obtaining for the cases studied, the best diaestereselection for the β-methyl substituted cyclohexenone. Also, in this particular case of good diaestereoselection, we could induce enantioinduction up to 73% ee by performing the borylation pathway with a (R,R)-QuinoxP type of ligand.

While screening the metal free context for this transformation, the acid catalyzed fluorination of the already formed β-borylated ketones was a key point. We formed an enol catalyzed by the acid that could interact with the electrophilic fluorinating reagent, and in this case, complete regioselection towards the α'fluoro β-boryl compounds was obtained. In those cases, diaestereoselection was close to 1/1.

As a limitation, the acid-catalyzed fluorination of β-borylated ketones could only be performed on linear ketones.

Eventually, we have been able to apply a new methodology towards the synthesis of α-fluoro and α'-fluoro β-boryl compounds with no precedents in the literature.

2.7 References

[1] a) T. L. Cottrell, *The Strengths of Chemical Bonds*, 2d ed., Butterworth, London, **1958**; b) B. Darwent, *National Standard Reference Data Series*, NationalBureau of Standards, no. 31, Washington, **1970**; c) S. W. Benson*, J. Chem. Educ.* **1965***, 42*, 502; d) J. A. Kerr, *Chem. Rev.* **1966**, *66*, 465.

[2] L. O. Brockway, *J. Am. Chem. Soc.* **1938**, *60*, 1348.

[3] M. Atsumi, P. Pykkö, *Chem. Eur. J.* **2009**, *15*, 12770.

[4] P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*. Wiley-VCH, **2004**.

[5] B. E. Smart, *J. Fluor. Chem.*, **2001**, *109*, 3.

[6] D. M. Lemal, *J. Org. Chem.* **2004**, *69*, 1.

[7] J. K. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev*, **1994**, *94*, 373.

[8] T. M. Anderson, I. Mudawar, *Transactions of the ASME*, **1989**, *111*, 752.

[9] C.A. Cox, R. L. Stavis, M. R. Wolfson, *Biol. Neonate, **2003**, 84*, 232.

[10] R. L. Stavis, M. R. Wolfson, C. Cox, N. Kechner, T. H. Shaffer, *Pediatric Research, **1998**, 43*, 132.

[11] C. I. Castro, J. C. Briceno, *Artif. Organs*, **2010**, *34*, 622.

[12] D.B. Harper, D. O'Hagan, Nat. Prod. Rep. **1994**, *11*, 4.

[13] C. Isanbor, D. O'Hagan, *J. Fluor. Chem.,* **2006**, *127*, 303.

[14] a) K. Müller, C. Faeh, F. Diedrich, *Science* **2007**, *317*, 1881; b) A. M. Thayer, *Chem. Eng. News*, **2006**, *84*, 15.

[15] W. R. Hasek, W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 543.

[16] W. J. Middleton, *J. Org. Chem*, **1975**, *40*, 574.

[17] G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem*, **1999**, *71*, 7048.

[18] a) T. Umemoto, R. P. Singh, Y. Xu, N. Saito, *J. Am. Chem. Soc.* **2010**, *132*, 18199; b) F. Beaulieu, L. –P. Beauregard, G. Courchesne, M. Couturier, F. Laflamme, A. L'Heureux, *Org. Lett.* **2009**, *11*, 5050; c) P. Tang, W. Wang, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 11482.

[19] a) W. C. Smith, C. W. Tullock, E. L. Muetterties, W. R. Hasek, F. S. Fawcett, V. A. Engelhardt, D. D. Coffman, *J. Am. Chem. Soc*. **1959**, *81*, 3165 b) W. R. Hasek, W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc*. **1960**, *82*, 543.

[20] A. Sutherland, J. C. Vederas, *Chem. Commun,* **1999**, 1739.

[21] C. Carpentier, R. Godbout, F. Otis, N. Voyer, *Tetrahedron Letters*, **2015**, *56*, 1244.

[22] A. I. Vogel, J. Leicester, W. A. Macey, *Org. Synth*, **1956**, *36*, 40.

[23] C. B. McPake, G. Standford, *Org, Process. Res. Dev.* **2012**, *124*, 10278.

[24] a) C. L. Liotta, H. P. Harris, *J. Am. Chem. Soc*. **1974**, *96*, 2250; b) J. H. Clark, *Chem. Rev.* **1980**, *80*, 429.

[25] D. W. Kim, C. E. Song, D. Y. Chi, *J. Am. Chem. Soc.* **2002**, *124*, 10278.

[26] G. Balz, G. Schiemann, *Chem. Ber.* **1927**, *60*, 1186.

[27] a) P. Barthazy, L. Hintermann, R. M. Stoop, M. Worle, A. Mezzetti, A. Togni, *Helv. Chim. Acta* **1999**, *82*, 2448; b) P. Barthazy, R. M. Stoop, M. Worle, A. Togni, A. Mezzetti, *Organometallics* **2000**, *19*, 2844; c) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160; d) S. -B. Zhao, R.-Y. Wang, H. Nguyen, J. J. Becker, M. R. Gagne, *Chem. Commun.* **2012**, *48*, 443.

[28] D. A. Watson, M. J. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661.

[29] T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 18106.

[30] A. Casitas, M. Canta, M. Sola, M. Costas, X. Ribas, *J. Am. Chem. Soc.* **2011**, *133*, 19386.

[31] P.S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 10795.

[32] M. A. Tius, *Tetrahedron* **1995**, *51*, 6605.

[33] a) E. Differding, H. Ofner, *Synlett.* **1991**, 187; b) R. E. Banks, S. N. Mohialdinkhaffaf, G. S. Lal, I. Sharif, R. G. Syvret*, J. Chem. Soc., Chem. Commun.* **1992**, 595; c) T. Umemoto, K. Tomita, *Tetrahedron Lett.* **1986**, *27*, 3271; d) S. Stavber, M. Zupan, A. J. Poss, G. A. Shia, *Tetrahedron Lett.* **1995**, *36*, 6769; e) J. R. Wolstenhulme, J. Rosenqvist, O. Lozano, J. Ilupeju, N. Wurz, K. M. Engle, G. W. Pidgeon, P. R. Moore, G. Sandford, V. Gouverneur, *Angew. Chem. Int. Ed*. **2013**, *52*, 9796.

[34] K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134.

[35] T. Furuya. H. M. Kaiser, T. Ritter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

[36] L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359.

[37] J. A. Ma, D. Cahrad, *Tetrahedron Asymmetry* **2004**, *15*, 1007.

[38] S. Suzuki, Y. Kitamura, S. Lectard, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 4581.

[39] N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728.

[40] J. Xu, Y. Hu, D. Huang, K. –H. Wang, C. Xu, T. Niu, *Adv. Synth. Catal.* **2012**, *354*, 515.

[41] D. Enders, M. R. M. Huttl, *Synlett.* **2005**, 991.

[42] T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826.

[43] M. Marigo, D. I. Fielenbach, A. Braunton, A. Kjoersgaard, K. A. Jorgensen*, Angew. Chem. Int. Ed.* **2005**, *44*, 3703.

[44] D. D. Steiner, N. Mase, C. F. Barbas, *Angew. Chem. Int. Ed.* **2005**, *44*, 3706.

[45] P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738.

[46] G. Stavber, M. Zupan, S. Stavber, *Tetrahedron Lett*. **2007**, *48*, 2671.

[47] E. Fuglseth, T. H. K. Thvedt, M. F. Moll, B. H. Hoff, *Tetrahedron* **2008**, *64*, 7318.

[48] G. Stavber, M. Zupan, S. Stavber, *Synlett.* **2009**, 589.

[49] T. Kitamura, K. Muta, *J. Org. Chem.* **2014**, *79*, 5842.

[50] S. Sato, M. Yoshida, S. Hara, *Synthesis* **2005**, 2602.

[51] N. Ahlsten, B. Martin-Matute. *Chem. Commun.* **2011**, *47*, 8331.

[52] Q. Yang, L. –L. Mao, B. Yang, S. –D. Yang, *Org. Lett.* **2014**, *16*, 3460.

[53] G. Verniest, E. Van Hende, R. Summont, N. De Kimpe, *Org. Lett.* **2006**, *8*, 4767.

[54] a) T. Fujiwara, T. Seki, M. Miura, Y. Takeuchi, Heterocycles **2009**, 79, 427; b) T. Seki, T. Fujiwara, Y. A. Takeuchi, *J. Fluorine Chem.* **2011**, *132*, 181.

[55] K. Sakthivel, P. D. Cook, *Synlett.* **2005**, 1586.

[56] W. Peng, J. M. Shreeve, *Tetrahedron Lett.* **2005**, *46*, 4905.

[57] a) Z. Guan, D. Wu, J. –P. Fu, Y. –H. He, *Heteroat. Chem.* **2010**, *21*, 250; b) J. –P. Fu, Y. –H. He, J. Zhong, Y. Yang, X. Deng, Z. Guan, *J. Fluorine Chem.* **2011**, *132*, 636.

[58] a) A. K. Gosh, B. Zajc, *Org. Lett.* **2006**, *8*, 1553; b) N. Allendörfer, M. Es-Sayed, M. Nieger, S. Bräse, *Synthesis* **2010**, 3439.

[59] J. Bi, Z. Zhang, Q. Liu, G. Zhang, *Green Chem.* **2012**, *14*, 1159.

[60] A. D. Dilman, P. A. Belyakov, M. I. Struchkova, D. E. Arkhipov, A. A. Korlyukov, V. A. Tartakovsky, *J. Org. Chem.* **2010**, *75*, 5367.

[61] S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu*, J. Am. Chem. Soc.* **2010**, *132*, 2856.

[62] J. Ramírez, E. Fernández, *Synthesis* **2005**, *10*, 1698.

[63] J. Ramírez, E. Fernández, *Tetrahedron Letters*, **2007**, *48*, 3841.

[64] S. Kindt, M. R. Heinrich, *Chem. Eur. J.* **2014**, *20*, 15344.

[65] L. Zhu, H. Chen, Z. Wang, C. Li, *Org. Chem. Front.* **2014**, *1*, 1299.

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

[67] M. T. Nguyen, A. F. Hegarty *J. Am. Chem. Soc.* **1984**, *106*, 1552.

[68] I. H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki *J. Am. Chem. Soc.* **2009**, *131*, 11664.

[69] R. Yazaki, T. Nitabaru, N. Kumagai, M. Shibasaki *J. Am. Chem. Soc*. **2008**, *130*, 14477.

[70] P. J. Duggan, M. Johnston, T. L. March, *J. Org. Chem.* **2010**, *75*, 7365.

[71] K. Lee, A. R. Zhugralin, A. H. Hoveyda *J. Am. Chem. Soc*., **2009**, *131*, 7253.

[72] A. Bonet, H. Gulyás, E. Fernández *Angew. Chem. Int. Ed.* **2010**, *30*, 5130.

[73] J. Liu, J. Chan, C. M. Bryant, P. A. Duspara, E. E. Lee, D. Powell, H. Yang, Z. Liu, Ch. Walpole, E. Roberts, R. A. Batey, *Tetrahedron Letters* **2012**, *53*, 2971.

[74] S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu*, J. Am. Chem. Soc.* **2010**, *132*, 2856.

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

The scientific man does not

Aim at an immediate result. He

Does not expect that his

Advanced ideas will be readily taken up.

His work is like that of a planter- for the future.

His duty is to lay the foundation

For those who are to come, and point the way

(Nicola Tesla)

3. Construction of vicinal C-B and C-X (X = Cl, Br) bonds.

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

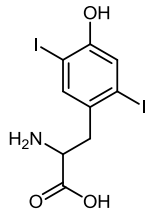
α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

3.1 Halogenated compounds (Halometabolites and organohalogens)

It's interesting to mention that whereas fluorinated-occurring molecules are rare (only eight examples found in nature), natural products containing halogens such as chlorine and bromine in their structure are quite spread. Several biologically active processes involve halogenation of molecular entities that later on play an important role in biology.

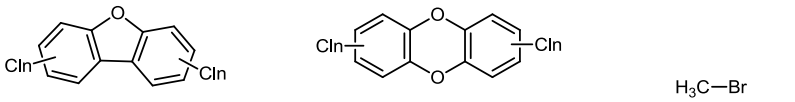
The first report of an halogen containing natural product (also called halometabolites) was that of a iodinated amino acid diiodotyrosine from the coral *Gorgonia cavolii* in the late 19th century[1](Figure 3.1).



Diiodotyrosine

Figure 3.1. *Diiodotyrosin structure.*

For many years, such compounds were considered rare and of little biological importance and there is still a perception that organohalogens present in the environment are of human origin only, however, well-known pollutants such as polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF) appear to be formed also naturally[2]. Even a significant proportion of a simple molecule, bromomethane, is produced by higher plants[3](Figure 3.2)



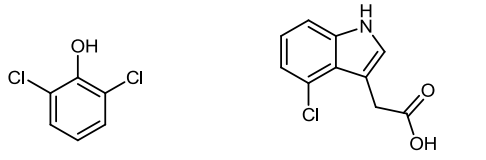
Polychlorinated dibezofuran (PCDD) | Polychlorinated dibenzodioxine (PCDD) | Bromomethane

Figure 3.2. *Structure of natural occuring halometabolites.*

Currently, it is known that there are over 3600 halogenated natural products from bacteria, fungi, algae, higher plants, and animals[4].

Chlorometabolites and bromometabolites predominate, whereas iodinated and fluorinated natural products are far less common. The functions of halometabolites are varied and they can have distinct physiological and biochemical roles.

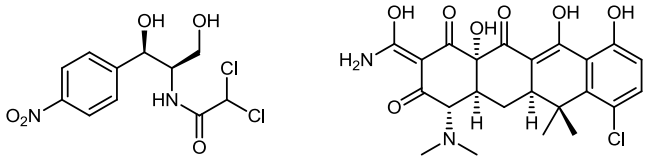
For instance, 2,6-dichlorophenol has a sex pheromone role[5], while 4-chloroindolyl-3-acetic acid is a plant growth hormone[6](Figure 3.3).



2,6-dichlorophenol 4-chloroindolyl-3-acetic acid

Figure 3.3. *Structure of natural occuring halometabolites.*

Several halometabolites, particularly those of marine origin, appear to have a defensive role[4], and a number of halometabolites isolated from bacteria and fungi have antibiotic activity, for example chloramphenicol and chlortetracycline (Figure 3.4).



Chloramphenicol Chlortetracycline

Figure 3.4. *Structure of Chloramphenicol and Chlortetracycline.*

The assumed role of many bacterial halometabolites by inhibiting the growth of competing organisms, has been questioned as these compounds are usually produced in very small quantities[7]. Nevertheless, their biosynthesis represents a considerable metabolic investment. Not only halometabolites found in nature offer special properties to their producing organisms. Artificially synthesized halometabolies (organohalogens) have been proven to offer important uses in industry and society.

To mention a couple of examples of halogen-containing compounds that are commercially available, Ceclor and Lorabid are used for treatment of ear infections[8]. Also, Toremifene is

used as a prostate cancer drug[9], or vancomacyn, which is used to fight penicillin-resistant infections[10](Figure 3.5).

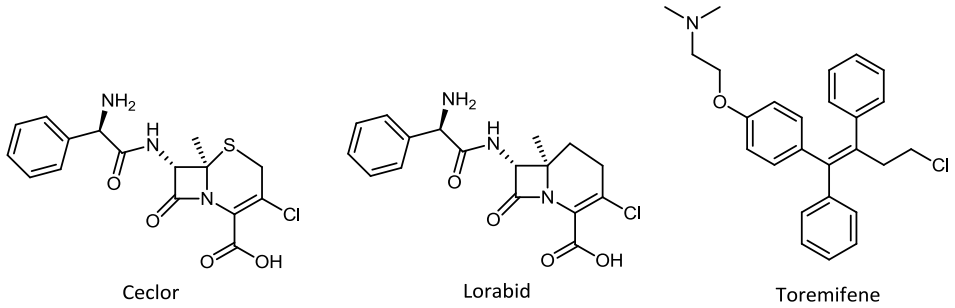


Figure 3.5. *Structure of Organohalogens used as drugs.*

Halogenated molecules are not only used for human health sciences, but also for the synthesis of materials. Vinyl chloride (CH_2=CHCl), which is a carcinogenic gas, is polymerized to polyvinyl chloride (PVC) as a plastic of great versatility and safety. PVC is a invaluable component of building materials, consumer goods, and medical equipment. More than 2.2 billion kilograms of PVC are used annually for wire, cable and other electrical applications[11](Figure 3.6).

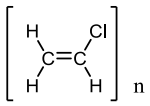


Figure 3.6. *Polyvinyl chloride.*

Also, more simple halogenated molecules as trichloroethylene (CHCl-CCl_2) and tetrachloroethylene (CCl_2-CCl_2) are widely used solvents in the dry cleaning industry[12].

It is worth noting that organohalogens are essential for crop production and protection as herbicides and insecticides. Ninety percent of grain farms utilize these chemicals in food production, even though some of them have been proven to have dangerous effects for humans in a long-term exposure[13](Figure 3.7).

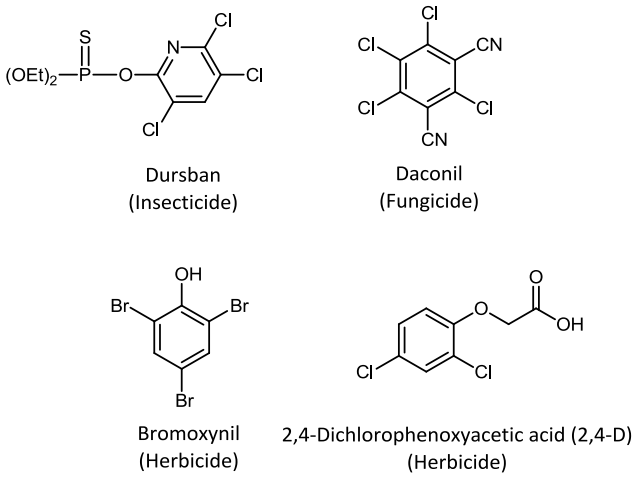


Figure 3.7. *Organohalogens used as pesticides.*

Another interesting family of halocarbons widely used, historically, are the chlorofluorocarbons (CFC's), which are strongly implicated in causing the ozone hole, and are being phased out as refrigerants, dry cleaning solvents, propellants, fire extinguishants and foam-bowing agents[14](Figure 3.8).

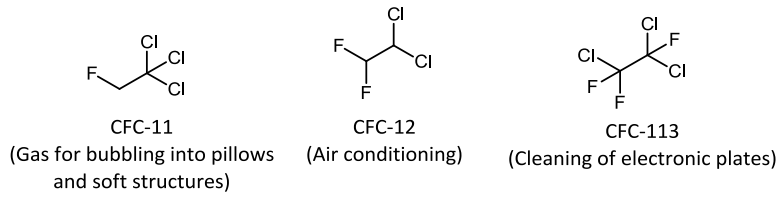


Figure 3.8. *Chlorofluorocarbons widely used in industry.*

At the moment, the replacement of this chemicals by hydrochlorofluorocarbons (HCFC's) and hydrofluorocarbons (HFC's) is being carried since the utilization of those chemicals has no impact on the stratospheric ozone and have low global warming potential[15](Figure 3.9).

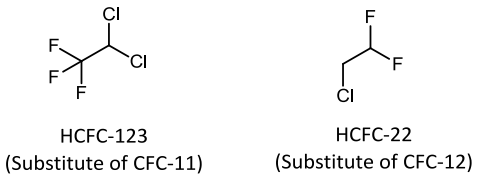


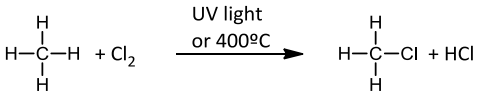
Figure 3.9. *Hydrochlorofluorocarbons used as CFC substitution.*

Although some synthetic organohalogens are toxic contaminants that need to be removed from the environment, the vast majority of organohalogens have little or no toxicity. Organic halogen compounds continue to play an essential role in human health and well-being, therefore, several methodologies towards their synthesis have been sought in industry as well as in academia.

3.2 Methodologies for preparation of C-X bonds (X = Cl, Br).

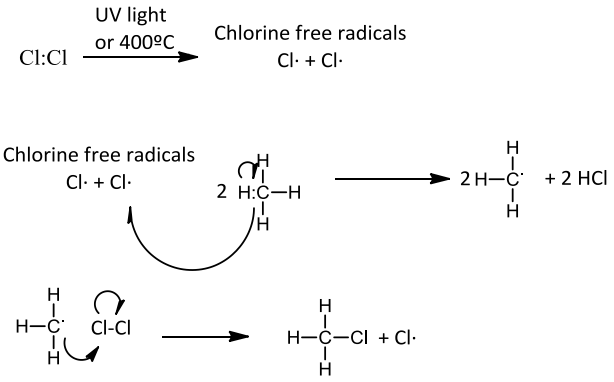
3.2.1 Chlorination and bromination of alkanes:

The chlorination of saturated aliphatic hydrocarbons has been historically achieved by free radical processes[16], where the reaction of an halogen (Cl_2) with an alkane is carried out in the presence of ultraviolet light or heat that leads to the formation of the haloalkane (Scheme 3.1).



Scheme 3.1. *Halogenation of methane.*

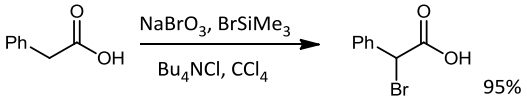
Experiments have shown that when an alkane and an halogen reactants are not exposed to the UV light or heat the reaction does not occur. However, once the reaction has started, the source of UV or heat can be removed. UV light contains enough energy to break the weaker non-polar X-X bonds. The fracture of the halogen molecule leads to the formation of two highly reactive chlorine free radicals. When a chlorine free-radical approaches a methane molecule, an homolytic fission of a C-H bond occurs. The chlorine free radical combines with the liberated hydrogen free radical to form hydrogen chloride and a methyl free radical (propagation step). Finally, the methyl free radical reacts with Cl_2 molecule to form chloromethane and a chlorine free radical that can continue the cycle (Scheme 3.2).



Scheme 3.2. *Radical chlorination of methane.*

Later on, ionic halogenation of alkanes has also been studied, giving however low yields of monobromides alongside polybromides and fragmentation products[17]. Also, aprotic organic super acids were shown to effectively catalyze ionic monobromination of C_4-C_7 n-alkanes and C_5-C_6 cycloalkanes[18], however, the formation of carbonyl containing compounds as by-products is the principal drawback for this strategy. Later on, Vol'pin and coworkers found out that ethane and cycloalkanes were selectively brominated using polihalomethane.2$AlBr_3$ under mild conditions[19].

The use of sodium bromate-trimethylsilyl bromide in conjunction with a phase transfer catalyst has been reported to give excellent yields of monobrominated molecules[20](Scheme 3.3).



Scheme 3.3. *Selective monobromination of alkanes.*

Recently the chlorination and bromination chemistry has evolved towards the need to use milder and more bench-stable reagents to afford halogenated products. This fact has led towards the production of literally dozens of different halogenating reagents, for chlorination and bromination[21]. Therefore we focus and discuss the reactivity of the reagents that we considered are the most typical, cheap and stable, which are N-Chlorosuccinimide (NCS) **105** and N-Bromosuccinimide (NBS) **106** (Figure 3.10).

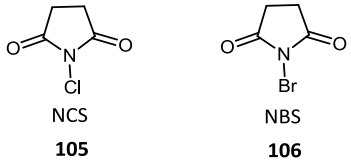
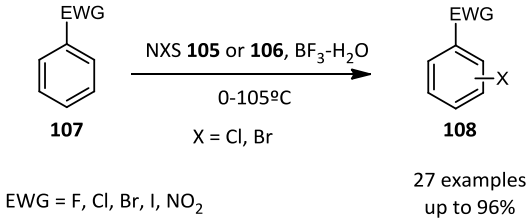


Figure 3.10. *Structure of NXS* ***105*** *and* ***106****.*

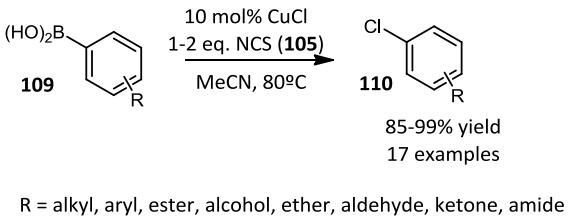
3.2.2 Chlorination and bromination reactions using bench-stable electrophilic halogenating reagents:

Concerning the halogenation of alkenes and arenes (Sp^2 C-C bonds) using the electrophilic chlorinating and brominating reagents, we can find few recent examples in the literature. NXS **105** and **106** were used towards the synthesis of halogenated aromatic compounds **108**, using BF_3-H_2O and trifluoromethanesulfonic acid to activate the N-halosuccinimides[22] obtaining in the cases studied the formation of the monohalogenated products in high selectivity and good yield (Scheme 3.4).



Scheme 3.4. *Electrophilic chlorination and bromination of aromatic compounds.*

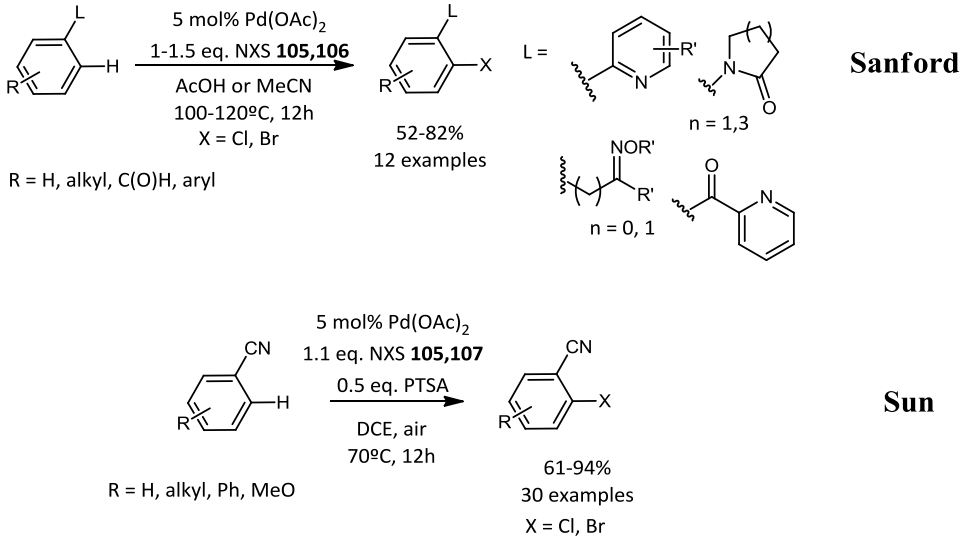
Hynes et al.[23] reported a mild and efficient Cu(I)-catalyzed methodology for the synthesis of aryl chlorides **110** from boronic acids **109**, since the aryl boronic acids are electron deficient. Under optimized conditions, up to 17 examples were successfully synthesized, ranging from 85 to 99% yield (Scheme 3.5).



Scheme 3.5. *Cu-catalyzed chlorination of arylboronic acids.*

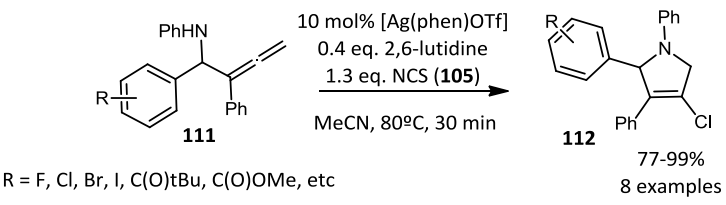
Aryl boron-bromide exchange is also efficient with NBS (**106**) for some substrates[24,25].

Pd has also been successfully used for the halogenation of aryl moieties using NCS (**105**) and NBS (**106**). Two examples by Sun and Sanford respectively[26] report the synthesis of halo aryls using $Pd(OAc)_2$, but in both cases they need a directing group (either amino or cyano groups). Sanford uses harsher reaction conditions whereas Sun reports lower reaction temperatures using substoichiometric amounts of *p*-toluenesulfonic acid (PTSA) and the advantage to run the reaction in an open air atmosphere. Both cases report good to excellent yields to products (Scheme 3.6).



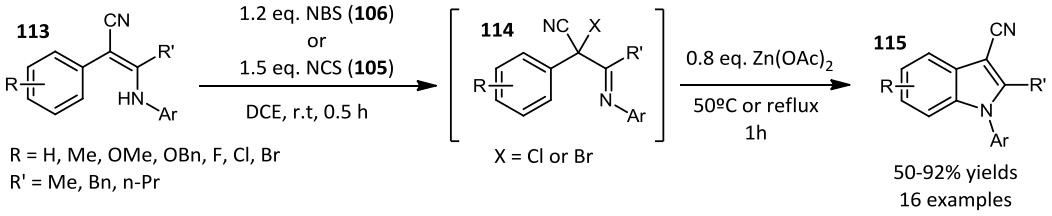
Scheme 3.6. *Pd-catalyzed chlorination and bromination of arenes.*

Also, intramolecular chloroamination can be achieved using NCS (**105**). Matsubara et al.[27] reported this reactivity using allenes **111** as substrates. The reaction conditions tolerate various functional groups. The vinyl silver intermediate reacts with the electrophilic halogenating source to obtain the corresponding haloamination product. The obtained pyrrole and pyrroline derivatives **112** are interesting intermediates since they bear a $C(sp^2)$-Cl bond, which can further react for a cross-coupling reaction to obtain the corresponding C-C bond derivatives (Scheme 3.7).



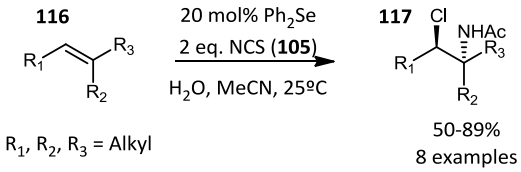
Scheme 3.7. *Intramolecular chloroamination of allenes.*

Quite recently, another interesting approach concerning the halogenation and cyclization of unsaturated compounds has been achieved. Zhao et al.[28] reported the synthesis of various N-arylindole-3-carbonitriles **115** in one pot from 2-aryl-3-arylamino-2-alkenenitriles **113** via in situ halogenation using electrophilic halogenating reagents (intermediate **114**). Many examples have been successfully synthesized and isolated with good to excellent isolated yields (Scheme 3.8).



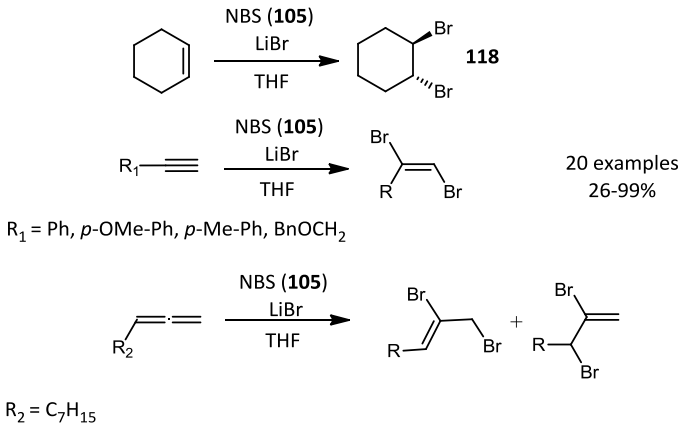
Scheme 3.8. *Oxidative cyclization of 2-aryl-3-arylamino-2-alkenenitriles.*

Also, not only chlorination of alkenes, but chloro-amination of alkenes **116** has been achieved using diphenyl selenide as a Lewis base catalyst[29]. The reaction conditions are mild and suitable for a wide range of substrates including those which are acid labile (Scheme 3.9). The amino-source in this case comes from the acetonitrile used as solvent.



Scheme 3.9. *Selenium catalyzed chloroamidation of olefins.*

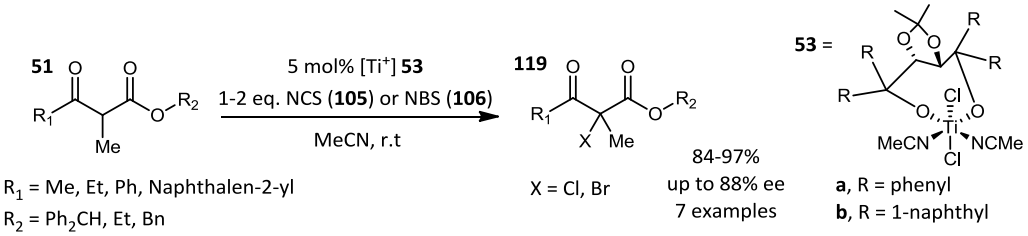
Dihalogenation of alkenes can also be achieved. In 2006, Shi et al.[30] reported the dibromination of alkenes, alkynes, allenes and methylenecyclopropanes (MCPs) within minutes using NBS (**106**) and LiBr in THF, room temperature in good to excellent yields (Scheme 3.10).



Scheme 3.10. *Dihalogenation of alkenes, alkynes and allenes using NBS (**106**) and LiBr.*

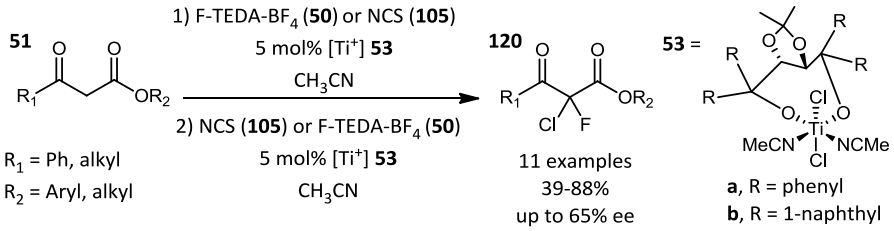
Another hot field in halogenation reactions is the α-chlorination and α-bromination of carbonylic compounds, due to the versatility this functionality has to offer, since α-halogenated carbonyl compounds can be converted into a diverse array of molecules[31]. Such benefits have generated considerable synthetic interest in metal catalysis and organocatalysis, as well as traditional methods such as the use of Lewis acids, and inorganic reagents[32].

Togni and coworkers reported the first catalytic enantioselective chlorination and bromination of β-keto esters[33a] in a similar way to the electrophilic fluorination of β-ketoesters[33b]. In this methodologies, chiral Ti^{2+} complexes **53** are used, and the substrate scope is limited to β-ketoesters since the catalyst needs of the two-binding points of the dicarbonylic compound (Scheme 3.11).



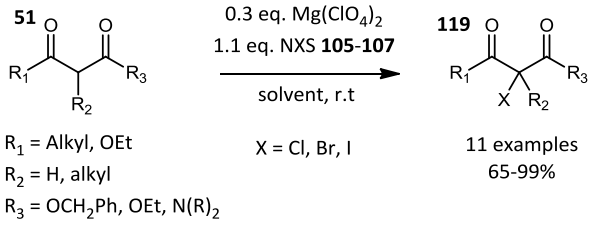
Scheme 3.11. *Titanium catalyzed enantioselectiva halogenation of β-ketoesters.*

Togni et al.[34] also proposed a very elegant work consisting on heterodihalogenation of β-ketoesters **51** using Ti^{2+} complexes **53** with F-TEDA-BF_4 (**50**) and NCS (**105**) to afford α-chloro-α-fluoro-β-ketoesters **120** in moderate to good yields. The sequence of the addition of the halogenating reagents determines the sense of the chiral induction (Scheme 3.12).



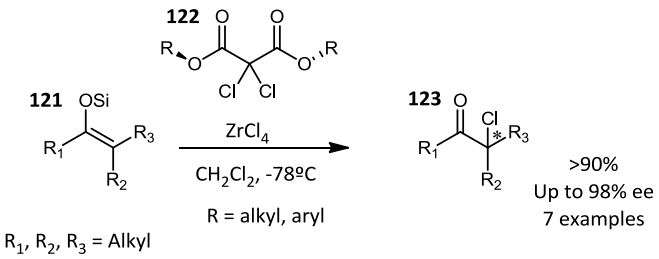
Scheme 3.12. *Ti-catalyzed geminal heterodihalogenation of β-ketoesters.*

Lewis acid catalyzed α-halogenation of dicarbonylic compounds has also been a sought methodology towards the obtantion of the titled products. Still in the field of dicarbonylic compounds, Lui et al.[35] reported a mild methodology of halogenation catalyzed by $Mg(ClO_4)_2$, yielding the corresponding products of chlorination and bromination in high to excellent yields under optimized conditions (Scheme 3.13).



Scheme 3.13. *$Mg(ClO_4)_2$ catalyzed α-halogenation of dicarbonylic compounds.*

Yamamoto et al.[36] reported the synthesis of α-haloketones using a stabilized enolate not formed in situ. This methodology involves the α-chlorination of silyl enolates catalyzed by $ZrCl_4$ using however a specific type of electrophilic halogenating reagent **122** instead of NCS (**105**). Excellent yields and also excellent enantioselectivities were obtained (Scheme 3.14). The chiral induction comes, in this case, from the electrophilic halogenating reagent.



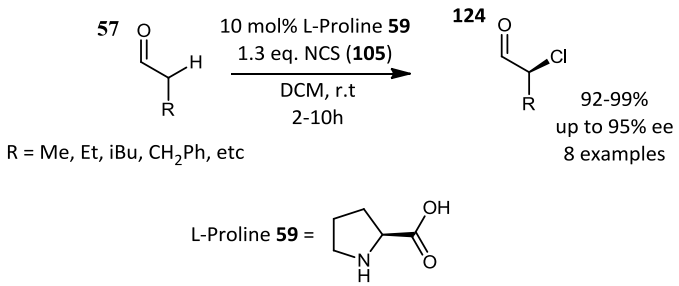
Scheme 3.14. *$ZrCl_4$-mediated α-chlorination of silyl enolates.*

Despite the mentioned reactivity, organocatalysis is the field that has focused more attention in the last decade to perform this transformation, since the substrate scope is generally

greater and the conditions milder. Besides, the two point-binding sites is not needed, whereas typically when Lewis acids are used for the synthesis of α-halogenated carbonyl compounds, 1,3-dicarbonylic compounds need to be used as substrates.

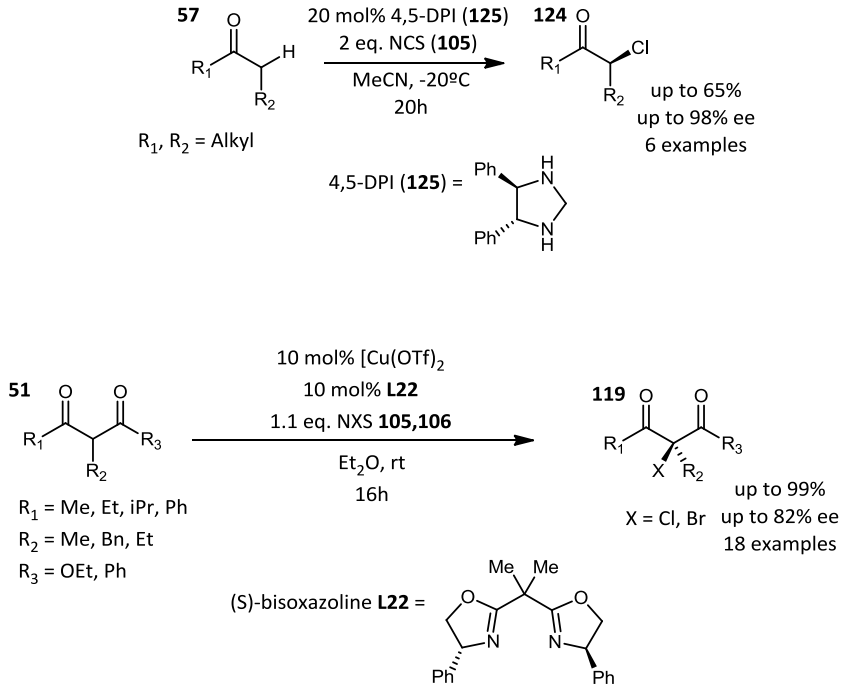
One of the first examples concerning catalytic enantioselective α-chlorination and α-bromination of carbonyl compounds was reported by Lectka et al.[37] using perhaloquinone-derived halogenation reagents and a chinchona alkaloid catalyst in a tandem halogenation/esterification of acid chlorides.

Also, the α-halogenation of carbonylic compounds using organocatalysts and NCS (**105**) as electrophilic reagent was reported by Jorgensen et al.[38]. Where they report direct organocatalytic asymmetric α-chlorination of aldehydes using NCS (**105**) as the chlorinating reagent and L-proline (**59**) as the organocatalyst. The α-chloro aldehydes were obtained in up to 99% yield and 95% ee (Scheme 3.15). Oxidation of the α-chloro aldehydes followed by esterification gave optically active α-chloro esters without loss of optical purity.



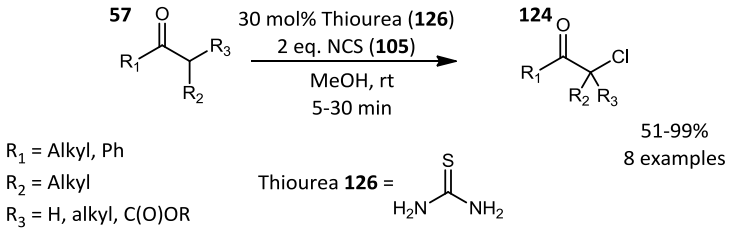
Scheme 3.15. *Proline-catayzed asymmetric α-chlorination of aldehydes.*

Similar work also performed by Jorgensen and coworkers concerning the organocatalytic α-chlorination of ketones **57**, using proline-based secondary amines as catalysts was reported almost timewise[39]. They have also successfully been able to electrophilically chlorinate and brominate β-ketoesters **51** using as a catalyst chiral bisoxaxolinecopper(I) complexes. In both cases good to excellent yields and enantioselectivities were obtained (Scheme 3.16).



Scheme 3.16. *Organocatalyzed halogenation of ketones and β-ketoesters.*

More recently, the α-chlorination of carbonylic compounds using NCS (**105**) has been described as the synthesis of α-chloroketones[40]. Also in this example, once the reaction conditions were optimized, up to 8 different chlorinated ketones were isolated in good yields but without any asymmetric induction (Scheme 3.17)

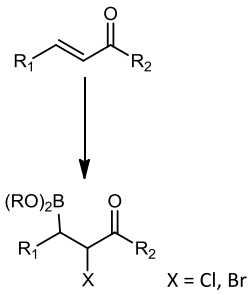


Scheme 3.17. *Thiourea catalyzed α-chlorination of ketones.*

3.3 Objectives of work

We wanted to screen methodologies to conduct chlorination and bromination of activated olefins with concomitant borylation, to finally obtain α-chlorinated and α-brominated β-borylated carbonyl compounds.

We have explored that the α-halogenation of carbonylic compounds is a feasible methodology to obtain α-haloketones, and we also know from our group that the β-boration of carbonylic compounds is a methodology to introduce nucleophilic boron functionalities on the β-position of carbonyl compounds.



The aim of this chapter is:

-Search for different methodologies that would allow us the obtantion of the desired final products.

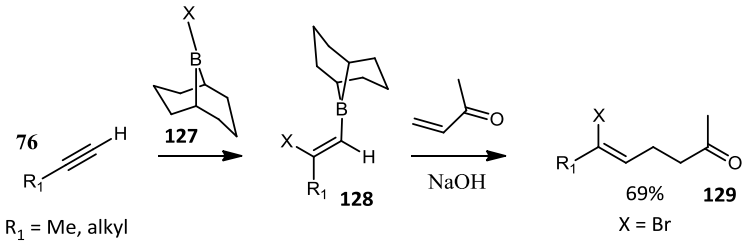
-Discuss which methodologies are suitable in terms of conversion and chemoselection.

-Explore the substrate scope concerning the obtantion of α-halo β-boryl ketones and its limitations.

The target compounds are not yet reported in the literature, therefore their synthesis will be very interesting because of the special properties that C-Cl and C-Br offer to their host molecules and also because of the versatility that the C-B bond has to offer.

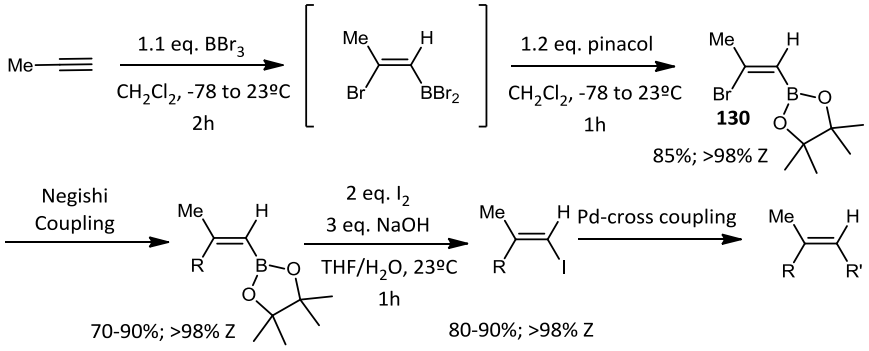
3.4 Results and discussion

To the best of our knowledge there are no reports in the literature concerning the haloboration of α,β-unsaturated ketones. However, there are a couple of examples on haloboration of alkenes and alkynes. Suzuki et al.[41] were one of the first to report a conjugate addition of B-(Z)-β-haloalkenyl-9-borabicyclo[3.3.1]nonanes (**128**) with acyclic α,β-enones to give (Z)-δ-halo-γ,δ-unsaturated ketones (**129**) (Scheme 3.18). To do so, they generated an haloborated intermediate compound through the haloboration of terminal alkynes **76** with B-bromo or B-iodo-9-boranicyclo[3.3.1]nonanes (**127**). The reaction proceed highly stereo- and regioselectively (>98%) to afford the *syn* adducts in essentially quantitative yields.



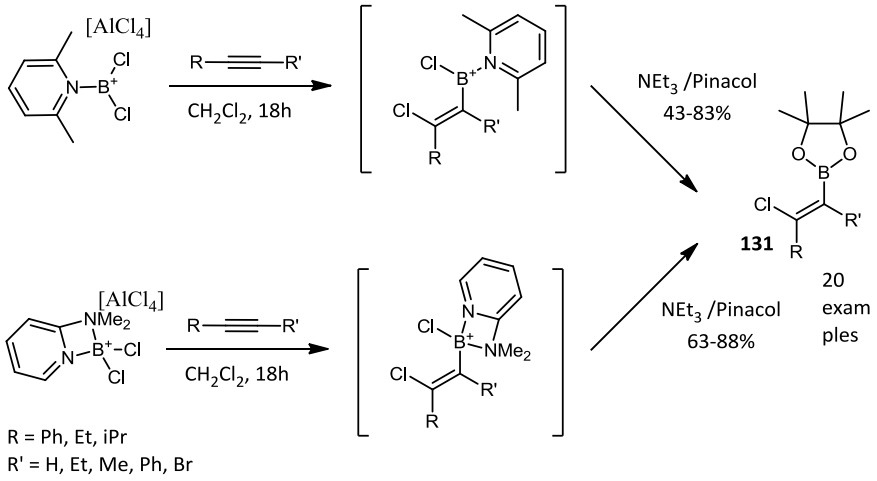
Scheme 3.18. *Haloboration and further homologation of terminal alkynes.*

More recently, Negishi et al.[42] reported the bromoboration of propyne to produce (Z)-2-bromo-1-propenyldibromoborane, which can be converted to the corresponding pinacolboronate **130** in high yields. The authors treated this intermediates for consecutive Negishi coupling to give trisubstituted (Z)-alkenylpinacolboronates containing various R groups in yields ranging 70 and 90%. Iodonolysis of the C-Bpin bond affords the alkenyl iodides in high yields and diaestereoselection, which can undergo Pd-cross coupling to obtain trisubstituted alkenes (Scheme 3.19).



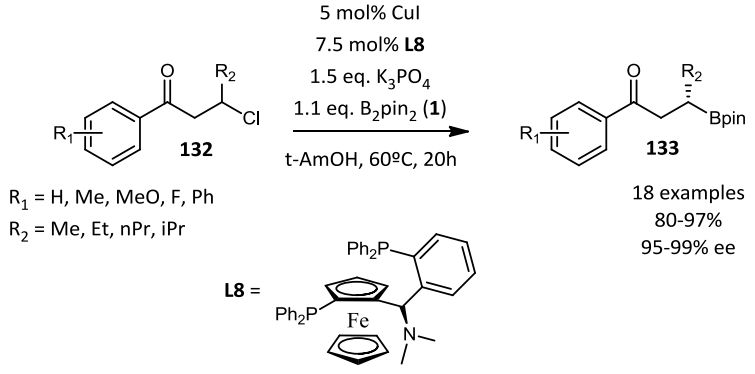
Scheme 3.19. *Synthesis of trisubstituted alkenes through haloboration as key step.*

Also, Ingleson et al.[43] reported an haloboration methodology to successfully haloborate internal alkynes, through an elegant design of boronium and borenium cations. In that context, dichloroborenium cations enable the chloroboration of internal alkynes regio- and stereospecifically. Also, further esterification on the boron moiety afford the corresponding trisubsubstituted vinyl pinacol boronate esters **131** obtained in good to high yield in all the internal alkynes studied (Scheme 3.20).



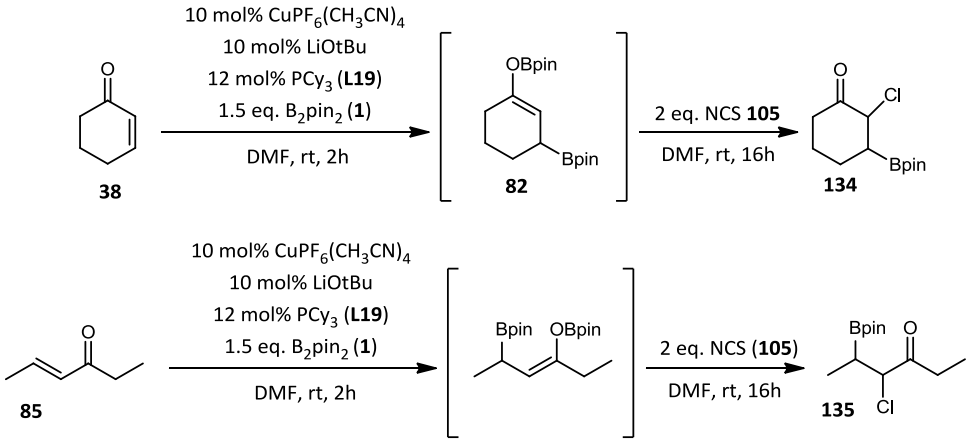
Scheme 3.20. *Haloboration of internal alkynes and subsequent esterification.*

In 2015 Yhu et al.[44] reported the use of β-chloroalkyl aryl ketones as precursors for the enantioselective boron conjugate addition reaction. Treatment of the β-chloroalkyl aryl ketone with a base, eliminates HCl and generates in situ the α,β-unsaturated ketone, that can be borylated. Using (S,S)-Taniaphos **L8** for optimized conditions, CuI, K_3PO_4 as the base and tert-Amyl alcohol (t-AmOH) as the solvent of choice, they obtained a vast array of β-borated ketones in high conversions and high enantioselectivities (Scheme 3.21).



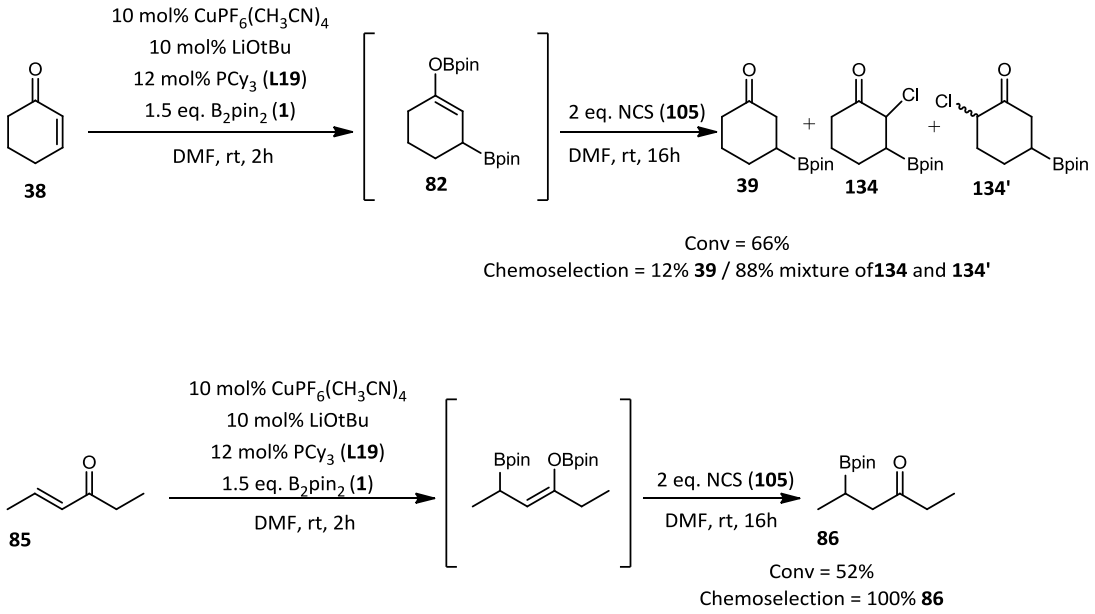
Scheme 3.21. *Asymmetric borylation of β-chloroalkyl aryl ketones.*

At that point, with all the precedents in hand, we explored different ways to finally obtain α-halo β-boryl ketones. Previous experience concerning the synthesis of Cα-F and Cβ-B ketones, led us to first attempt methodologies similar to the ones used for the α-fluorination β-borylation of carbonyl compounds, but instead of using F-TEDA-BF_4 (**50**), we used the most standard electrophilic halogenating reagents NCS (**105**) and NBS (**106**) (Scheme 3.22). Mechanistically, we envisaged that we would form the 1,4-diborated intermediate, which is nucleophilic, and would perform similar reactivity with the chosen electrophilic chlorinating reagent. For the screening of conditions, we used as model substrates 2-cyclohexen-1-one (**38**) and 4-hexen-3-one (**85**) and NCS (**105**) as the halogenating reagent.



Scheme 3.22. *Cu-catalyzed borylation/chlorination of* ***38*** *and* ***85****.*

Interestingly, applying the same conditions for both substrates that led towards the successful borylation/fluorination, in this case, the halogenation was not selective. Particularly, in the case of **38**, 66% conversion of substrate towards products was achieved (remaining 34% of 2-cyclohexen-1-one unreacted). The 66% converted products were identififed to be 12% of hydroborated product **39**, and 88% towards a regioisomeric mixture of chlorinated compounds **134** and **134'**, as it could be seen by ^{1}H NMR spectroscopy and GC analysis. Similar to the not optimized conditions of fluorination/borylation, the mixture of chlorinated compounds are those in which the halogen has been attached to both sides of the carbonylic compound, meaning α and α' position. In the case of the substrate 4-hexen-3-one (**85**), the halogenation didn't take place, obtaining in the end exclusively α-protonated β-borated compound in moderate conversion (Scheme 3.23).



Scheme 3.23. *Cu-catalyzed borylation/chlorination of **38** and **85**.*

At that point, we wanted to test if those results were a matter of lack of reactivity of the substrate that was not suitable for the electrophilicity of the new reagent. Therefore, we explored alternative α,β-unsaturated carbonyl compounds to test our methodology that worked for the α-fluorination β-borylation(Table 3.1).

Chalcone **5b** led to poor conversion values but complete chemoselection towards the αH /βB compound (Table 3.3 entry 1). Substrates **5a**, **136** and **137** which only differ on the aryl ring substitution also led to similar high conversion values and complete chemoselection towards the α-protonated β-borated compounds (Table 3.3 entries 2-4), and not even traces of the corresponding halogenated product could be detected. Also linear substrates similar to 4-hexen-3-one **85**, but with longer aliphatic chains such as 3-hepten-2-one (**91**) and 4-nonen-3-one (**138**), led to moderate and good results in terms of conversion but again complete chemoselection towards the protonated product (Table 3.1 entries 5 and 6).

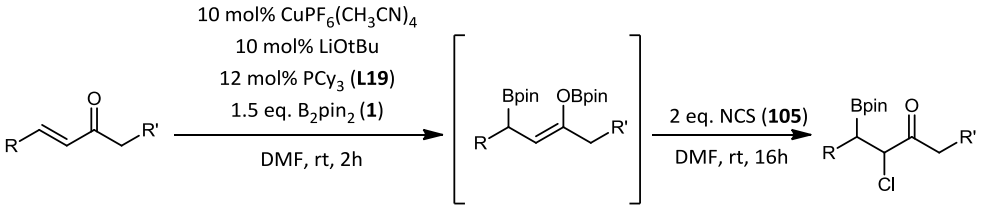
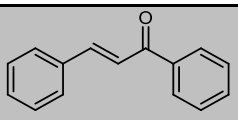
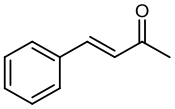
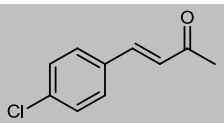
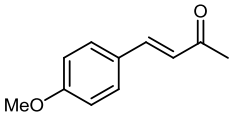
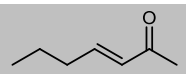
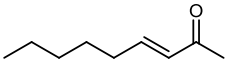


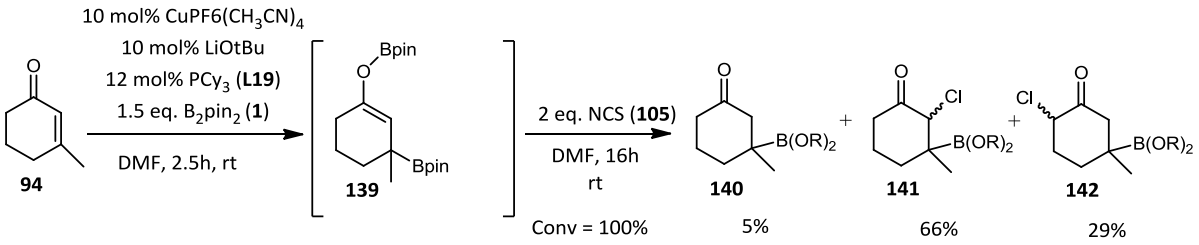
Table 3.1. *Substrate reactivity towards standard borylation/halogenation methodology.*

Entry	Substrate	Conv(%)b	αCl/βB(%)[b]	αH/βB(%)[b]
1[a]	 **5b**	20	0	100
2[a]	 **5a**	95	0	100
3[a]	 **136**	95	0	100
4[a]	 **137**	90	0	100
5[a]	 **91**	55	0	100
6[a]	 **138**	86	0	100

[a]Standard conditions: $CuPF_6$ (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.03 mmol), DMF (2 mL) the α,β-unsaturated ketone used as substrate (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NCS (**105**) (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. [b]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

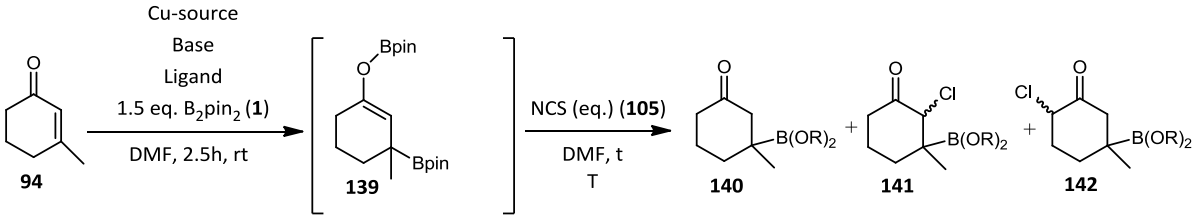
So far, moderate results have been obtained concerning the only cyclic substrate studied 2-cyclohexen-1-one (**38**), even though the regioselection of the corresponding halogenated-borylated compound was bad. Therefore, we decided to screen other cyclic substrates, in this case, β-substituted substrates. We performed the screening of conditions using 3-methyl-2-cyclohexen-1-one (**94**), which also gave us good results in the fluorination/borylation methodology.

Interestingly, applying the same conditions that worked for the fluorination/borylation of 3-methyl-2-cyclohexen-1-one (**94**), here we obtained promising results (conditions in Table 3.2). Conversion was complete and chemoselection was around 95%, but in this case only 2 regioisomers were obtained, and identified to be the α-chloro-β-boryl cycloenone **141** and α'-chloro β-boryl cycloenone **142** (Scheme 3.24).



Scheme 3.24. *Cu-catalyzed borylation/halogenation of* ***94****.*

With this preliminary result in hand, we were encouraged to change conditions in order to favor the formation of one single regioisomer. We first studied the effect of the equivalents of the electrophilic chlorinating reagent and the reaction time. Results are summarized in Table 3.2. We considered that tuning the equivalents of the chlorinating reagent would favor the formation of one single regioisomer. Decreasing the quantity down to one equivalent (Table 3.2 entry 2) led to the formation of considerable amounts of α-protonated compound, and increasing up to 3 equivalents, even though chemoselection was complete towards halogenated/borylated compounds, the regioselection was still present in considerable amounts (Table 3.2, entry 3). Concerning the reaction time, we studied the halogenation time, and we decreased down to 4h, obtaining significant amounts of protonation/borylation. 5h already gave similar results to the standard 16h time used previously (Table 3.4 entries 4-5). Increasing up to 24 hours didn't lead to any improvement concerning chemoselection nor regioselectivity (Table 3.2 entry 6).



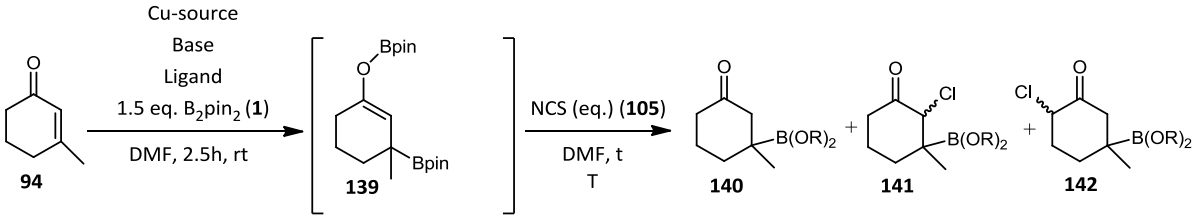
94 139 140 141 142

Table 3.2. *Screening conditions for the Cu-catalyzed borylation/halogenation of* ***94****.*

Entry	t(borylation/ chlorination)	NCS(eq)	Conv(%)[b]	140(%)[b]	141(%)[b]	142(%)[b]
1[a]	2.5h/16h	2 eq.	100	5	66	29
2[a]	2.5h/16h	1 eq.	100	64	28	8
3[a]	2.5h/16h	3 eq.	100	0	67	33
4[a]	2.5h/4h	2 eq.	100	85	12	2
5[a]	2.5h/5h	2 eq.	100	10	59	31
6[a]	2.5h/24h	2 eq.	100	9	66	25

[a]Standard conditions: $CuPF_6$ (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.025 mmol), DMF (2 mL) the α,β-unsaturated ketone **94** (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NCS (**105**) (0.25-0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 4 to 24 hours. [b]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

We also wanted to screen if the metal source and different ligands had any effect in comparison to the standard conditions (Table 3.3). Changing $CuPF_6(CH_3CN)_4$ to CuCl led towards the formation of only 15% halogenated products (Table 3.3 entry 1 *vs*. 2). Also, CuOTf was neither a good approach, since the reaction outcome was towards the obtantion of the α-protonated β-borylated compound **140** and only traces of the halogenated ones (Table 3.3 entry 3). This results are in agreement that $CuPF_6(CH_3CN)_4$ is crucial for the formation of the 1,4-diborated-enolate-type of intermediate needed to carry electrophilic trappings other than protons. Concerning the ligands, the use of PPh_3 (**L21**) instead of PCy_3 (**L19**) led to similar results in terms of chemoselection and regioselectivity (Table 3.3 entry 4). However, bulkier ligands such as Rac-BINAP (**L24**) and dppp (diphenylphosphino propane) (**L20**) led towards the obtantion of greater amounts of α-protonated β-borylated compound (Table 3.3 entries 5 and 6).



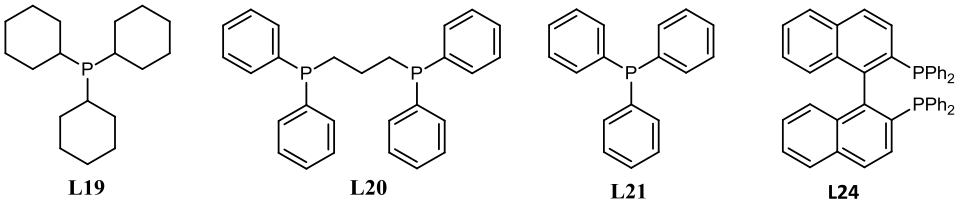


Table 3.3. *Screening conditions for the Cu-catalyzed borylation/halogenation of* ***94****.*

Entry	Cu(I)(%)	Ligand(%)	Conv(%)[b]	140(%)[b]	141(%)[b]	142(%)[b]
1[a]	$CuPF_6(CH_3CN)_4$ (10)	**L19** (12)	100	5	66	29
2[a]	CuCl (10)	**L19** (12)	100	85	12	5
3[a]	CuOTf (10)	**L19** (12)	100	99	traces	traces
4[a]	$CuPF_6(CH_3CN)_4$ (10)	**L21** (12)	100	8	63	29
5[a]	$CuPF_6(CH_3CN)_4$ (10)	Rac-BINAP **L24** (12)	100	80	19	1
6[a]	$CuPF_6(CH_3CN)_4$ (10)	**L20** (12)	100	99	traces	traces

[a]Standard conditions: Cu(I) (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), **L19, L20, L21** or **L24** (0.025 mmol), DMF (2 mL) the α,β-unsaturated ketone **97** (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NCS (**105**) (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. [b]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

We last wanted to focus on the solvent and the bases (Table 3.4). The other solvent of use that we could utilize similar to DMF in terms of polarity and aproticity is DMSO. Changing DMF by DMSO led to very poor chemoselections but the regioselectivity was complete towards the α-chloro β-boryl ketone (Table 3.4 entry 2). Increasing the reaction time or the amount of chlorinating reagent favored slightly better results in terms of chemoselection, but still not satisfactory (Table 3.4 entries 3 and 4). Surprisingly, substituting the base LiOtBu by Cs_2CO_3 and NaOtBu led to similar results in terms of conversion, chemoselection and regioselection, but still regioselection was far from good (Table 3.4 entries 5 and 6).

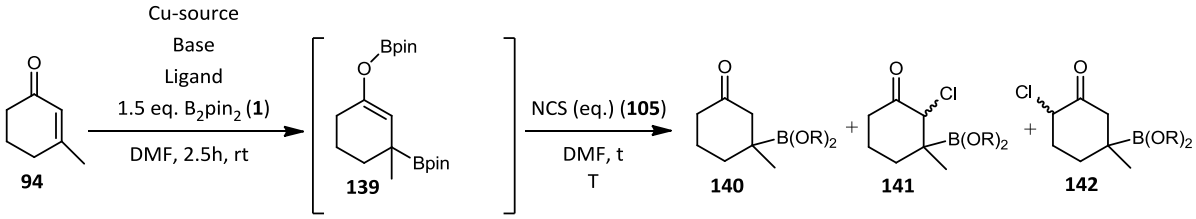


Table 3.4. *Screening conditions for the Cu-catalyzed borylation/halogenation of* ***94****.*

Entry	Base(%)	Solvent	t(borylation/ chlorination)	NCS(eq)	Conv(%)[b]	140(%)[b]	141(%)[b]	142(%)[b]
1[a]	LiOtBu (10)	DMF	2.5h/16h	2 eq.	100	5	66	29
2[a]	LiOtBu (10)	DMSO	2.5h/16h	2 eq.	100	90	10	0
3[a]	LiOtBu (10)	DMSO	2.5h/48h	2 eq.	100	86	14	0
4[a]	LiOtBu (10)	DMSO	2.5h/16h	3 eq.	100	82	18	0
5[a]	Cs_2CO_3 (10)	DMF	2.5h/16h	2 eq.	100	14	56	30
6[a]	NaOtBu (10)	DMF	2.5h/16h	2 eq.	100	6	71	23

[a]Standard conditions: Cu(I) (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.03 mmol), DMF or DMSO (2 mL) the α,β-unsaturated ketone **97** (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NCS (**105**) (0.5-0.75 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16-48 hours. [b]Conversion and selectivity determined by ^{1}H NMR spectroscopy and GC analysis.

With the screened conditions in hand, we wanted to move towards other β-substituted cyclohexenones, to see if there's an influence on the β-substitution concerning the conversion, chemoselection and regioselection of the reaction. We screened different β-aryl substituted cyclohexenones, and we were glad to discover that within this very concrete examples, excellent conversions were obtained, as well as moderate to good chemoselections, and also, one single regioisomer was seen in all cases, which was the α-halogenated β-borylated regioisomer. This methodology could also be extended to the utilization of NBS (**106**) as bromination reagent. Results are summarized in Table 3.5 and Table 3.6.

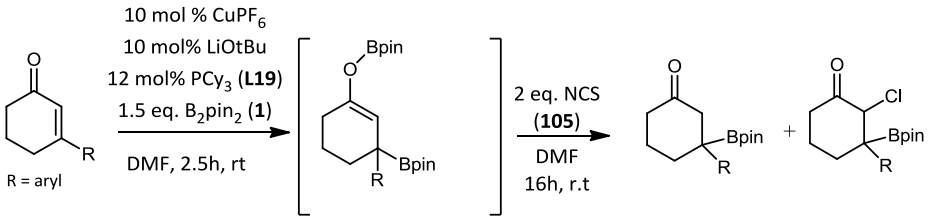
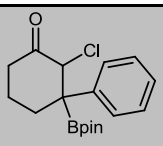
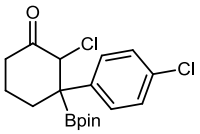
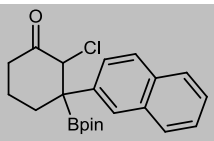
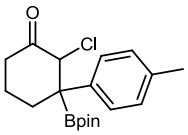
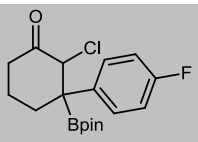
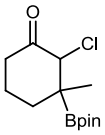


Table 3.5. *Cu-catalyzed borylation/halogenation of β-substituted cyclic enones.*

Entry	Product	Conv(%)[b]	Chemo(%)[b]	I.Y.(%)
1[a]	 **143**	100	44	30
2[a]	 **144**	100	99	73
3[a]	 **145**	100	66	50
4[a]	 **146**	100	55	37
5[a]	 **147**	100	73	62
6[a]	 **142**	100[c]	95	79

[a]Standard conditions: Cu(I) (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.03 mmol), DMF (2 mL) the β-substituted α,β-unsaturated ketone (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NCS (**105**) (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. [b]Conversion and chemoselection determined by ^{1}H NMR spectroscopy and GC analysis. [c]Obtained as a regioisomeric mixture of products α-Cl /α'-Cl (68/32).

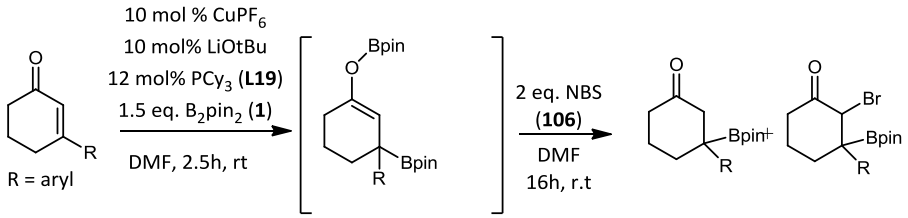
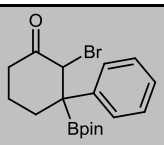
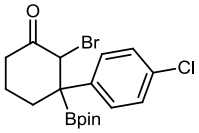
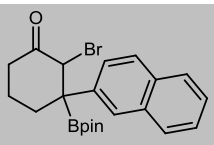
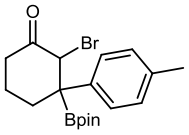
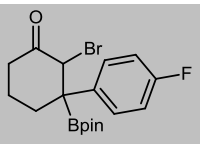
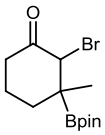
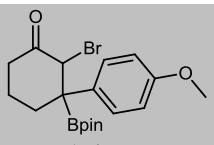


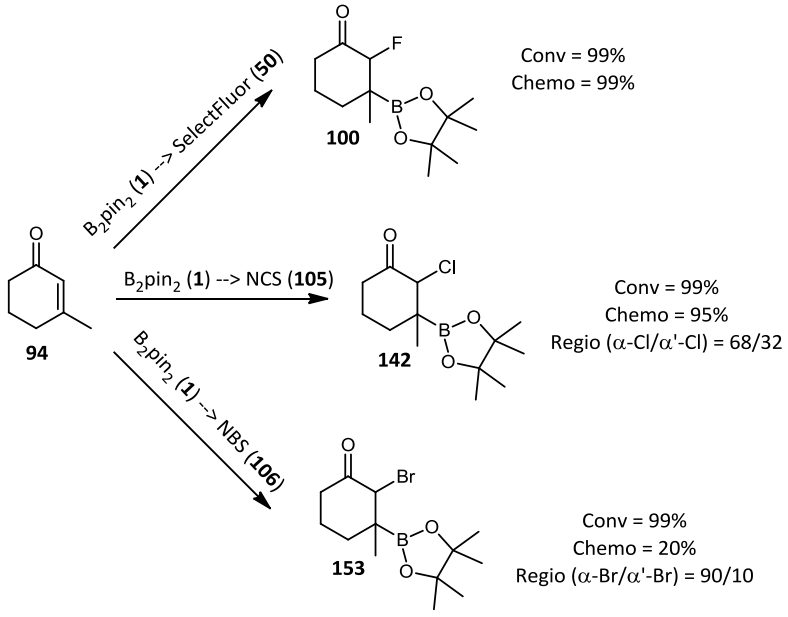
Table 3.6. *Cu-catalyzed borylation/halogenation of β-substituted cyclic enones.*

Entry	Product	Conv(%)[b]	Chemo(%)[b]	I.Y.(%)
1[a]	 **148**	100	20	10
2[a]	 **149**	95	70	57
3[a]	 **150**	100	50	27
4[a]	 **151**	100	40	20
5[a]	 **152**	100	35	17
6[a]	 **153**	100[c]	20	13
7	 **154**	100	61	47

[a]Standard conditions: Cu(I) (0.025mmol), B_2pin_2 (**1**) (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (**L19**) (0.025 mmol), DMF or DMSO (2 mL) the β-substituted α,β-unsaturated ketone (0.25 mmol). The reaction was stirred at room temperature for 2.5 hours. Afterwards, the NBS (**106**) (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. [b]Conversion and chemoselection determined by ^{1}H NMR and GC analysis. [c]Obtained as a regioisomer mixture of products α-Br /α'-Br (90/10).

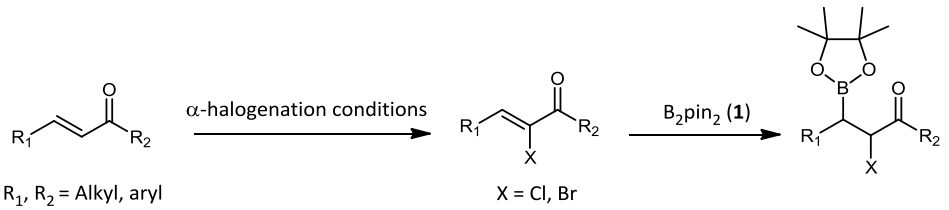
All the β-aryl substituted cyclohexenones studied have efficiently conducted the borylation/chlorination and bromination of the mentioned substrates. Similar trends of chemoselection were seen in all the examples, with special emphasis that the electronwithdrowing aryl groups, led to higher degree of chemoselection and therefore isolated yield (products **144**, **149** and **147**, **152**). Interesting to note that despite the steric bulk of the naphthyl substituent, products **145** and **150** were quantitatively formed. When the steric bulk of the halogen itself increases, the chemoselection drops, as it can be seen for all the examples if we compare the chlorinated with the brominated products (Table 3.6 vs. Table 3.7). Under identical conditions, the brominations offered less chemoselection towards the desired products. 3-methyl-2-cyclohexen-1-one **94** that was used as model substrate for chlorination, when submitted to bromination conditions with NBS, the chemoselectivity also droped even though the regioselection was majoritary towards the α-bromo β-boryl compound (product **153**). Finally, substrate bearing a *p*-MeO group could be cleanly brominated (product **154**), but when submitted to chlorination conditions, the regioselection was very poor and we couldn't isolate any clear compound.

Interestingly, if we take substrate **94**, which has been successfully halogenated and borylated with Selectfluor (**50**), NCS (**105**) and NBS (**106**), we see a tendency where the halogenation is more effective with **50**, obtaining high degree of conversion and chemoselection, whereas using NCS and NBS **105** and **106** respectively, the chemoselection and regioselection is lower, probably due to the increasing steric bulk of the halogens as we go down the periodic table (F<Cl<Br) (Scheme 3.25).



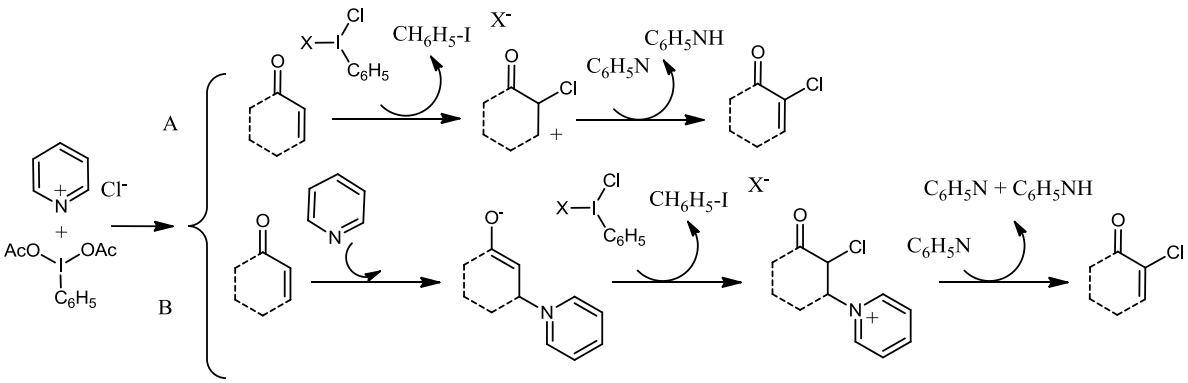
Scheme 3.25. *Halogenation reactivity of substrate **94** with **50**, **105** and **106**.*

At that point, encouraged by the results, we wanted to approach this issue from another perspective, to screen if we could halogenate and borylate the substrates that were not successfully haloborated using the Cu-catalyzed methodology. We therefore thought about halogenating the α,β-unsaturated carbonyl compounds on the α-position, to obtain the corresponding α-chloroenones. Once obtained, then submit the α-chloroenones to borylation conditions to yield our desired final product (Scheme 3.26).



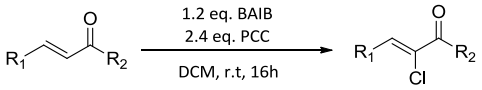
Scheme 3.26. *Envisaged pathway for sequential halogenation /borylation of α,β-unsaturated carbonyl compounds.*

Towards this end, we based the synthesis of α-chloroenones in a previously reported methodology using bisacetoxyiodobenzene (BAIB) and pyridinium chlorochromate (PCC)[45]. Concerning the mechanism of the reaction, it is postulated to potentially follow one of the two pathways. In both cases, oxidation of Py.HCl (which is in situ generated from PCC) and bisacetoxy iodobenzene (BAIB) generated an electrophilic chlorine source (Scheme 3.27). In pathway A, reaction of this species with α,β-unsaturated carbonyl compounds forms a carbocation on the β-position, which followed by deprotonation, forms the α-chlorinated product. Alternatively in pathway B, the α,β-unsaturated carbonyl compound is activated by pyridine, providing a β-pyridinium enolate which upon reaction with the previously in-situ formed electrophilic chlorine source gives intermediate β-pyridinium α-chloro compound, which upon elimination generates the α-chloroenone.



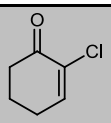
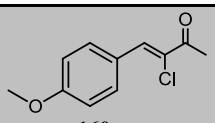
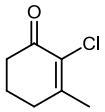
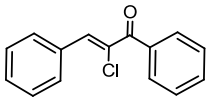
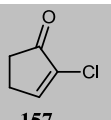
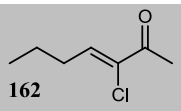
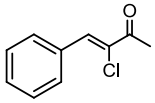
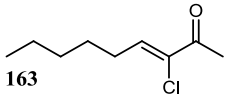
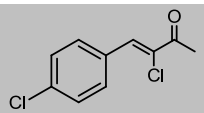
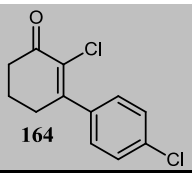
Scheme 3.27. *Mechanism for the α-chlorination of α,β-unsaturated carbonyl compounds.*

Applying the reported methodology to our model α,β-unsaturated ketones, we successfully obtained up to 10 diferent α-haloketones. Results are summarized in Table 3.7.



R_1, R_2 = Alkyl, aryl

Table 3.7. *Synthesis of α-chloroenones.*

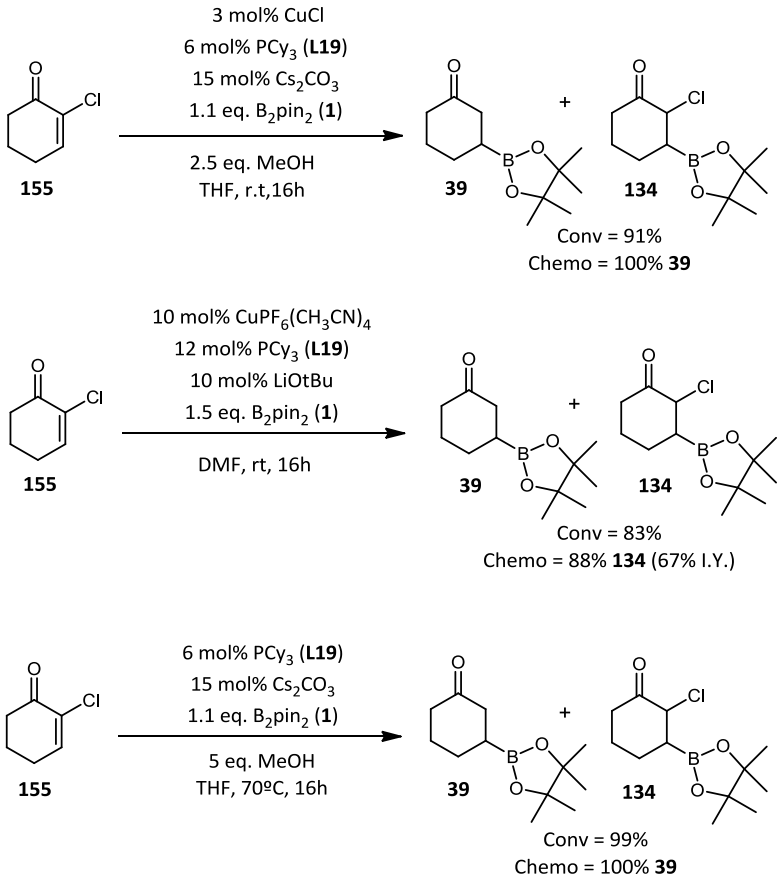
Entry	Product	Conv(%)[b]	I.Y.(%)	Entry	Product	Conv(%)[b]	I.Y.(%)
1[a]	 **155**	81	67	**6**[a]	 **160**	76	50
2[a]	 **156**	99	54	**7**[a]	 **161**	75	43
3[a]	 **157**	70	45	**8**[a]	 **162**	60	50
4[a]	 **158**	62	30	**9**[a]	 **163**	54	44
5[a]	 **159**	46	32	**10**[a]	 **164**	69	40

[a]Standard procedure: A magnetically stirred solution of α,β-unsaturated ketone (0.518 mmol), CH_2Cl_2 (4mL), BAIB (bisacetoxyiodobenzene)(0.60 mmol), PCC (pyridinium chlorochromate) (1.25 mmol), rt, 16h. [b]Conversion determined by ^{1}H NMR spectroscopy and GC analysis.

Up to 10 different enones were successfully halogenated, being products **160**, **162**, **163** and **164** for the first time reported in the literature. Special emphasis on the synthesis of **164**, which the corresponding non-halogenated α,β-unsaturated analogue could be cleanly α-chlorinated β-borated in high conversion and chemoselectivity (see Table 3.5 entry 2).

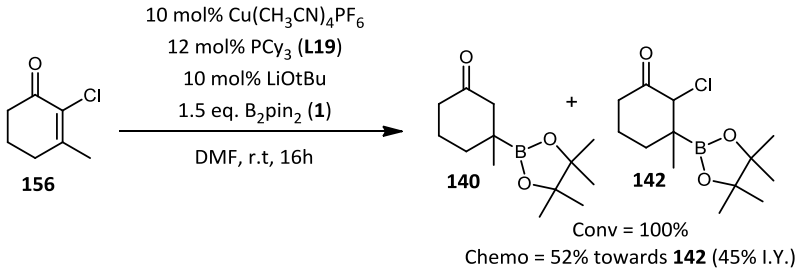
Now, with our α-chloroenones in hand, we studied if we could conduct the borylation of those substrates to finally obtain the α-chlorinated β-borylated compounds. We started with substrate **155**, and we submitted it to the typical β-borylation conditions, using THF and MeOH as protic additive, and CuCl as the metal source. Interestingly, the reaction led to high values of conversion, but chemoselectivity was complete towards the α-protonated β-borylated

compound **39**, with no formation of the α-chlorinated β-borylated produt. However, changing conditions towards the proton-free conditions using $CuPF_6(CH_3CN)_4$, LiOtBu in DMF, led towards the formation of the desired compound **134**, in high yields, and as one single regioisomer (Scheme 3.28). However, the chemoselection was not complete, and 22% of products consisted on the α-protonated β-borylated ketone **39**. Also, in the metal free context, high conversion but exclusive obtantion of α-protonated β-borylated compound was obtained.



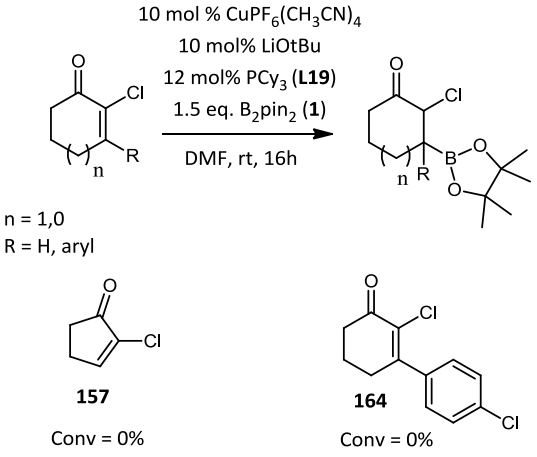
Scheme 3.28. *Borylation of α-chloroenones.*

Encouraged by the results concerning the $CuPF_6$ methodology, we screened if the rest of the substrates synthesized could be as well borylated using this methodology. Subtrate **156** bearing 3-methyl substitution was also quantitatively borylated, but chemoselection was slightly lower (52%)(Scheme 3.29).



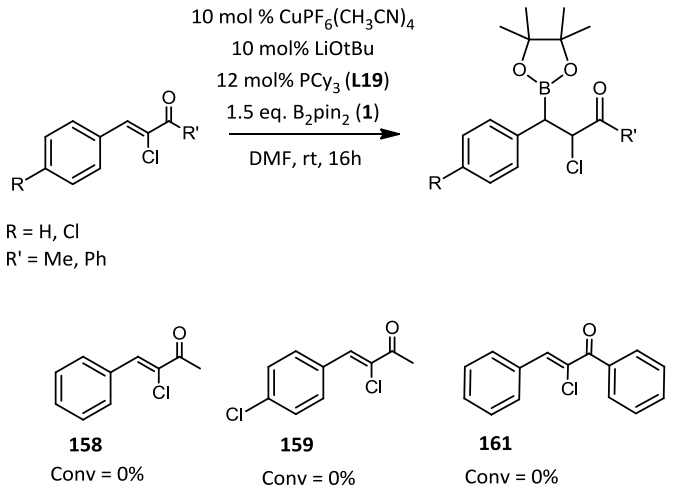
Scheme 3.29. *Borylation of 2-chloro-3-methyl-2-cyclohexen-1-one (**156**).*

Unfortunately, cyclic substrates **157** and **164**, led to no conversion to any product, only halogenated ketone could be recovered (Scheme 3.30). We consider that the steric bulk generated by the halogen in the α-position in this case favors the non-reactivity for the borylation. Actually, substrate **164** was prepared from 3-(*p*-chlorophenyl)-cyclohexen-2-one, that could be successfully borylated and halogenated in one step using the Cu-catalyzed borylation/halogenation methodology to obtain the product **144**.



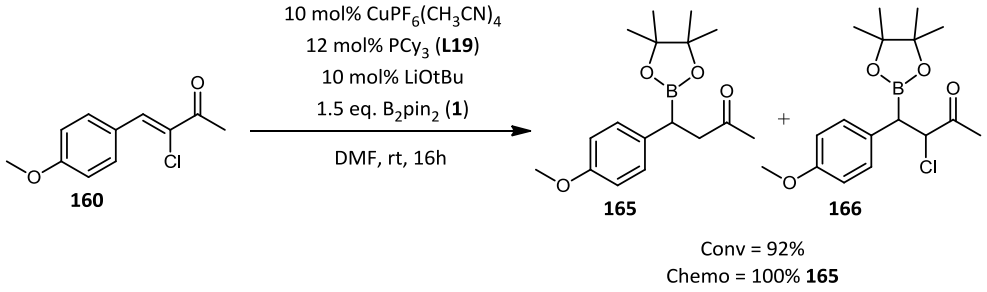
Scheme 3.30. *Borylation of α-chlorocycloenones **157** and **164**.*

Also, the chlorinated chalcone **161** and all the chlorinated 4-phenylbut-3-en-2-one bearing different substitution on the aromatic ring **158** and **159**, could not be successfully borylated. Substrates **161**, **158** and **159** gave no conversion to any product (Scheme 3.31).



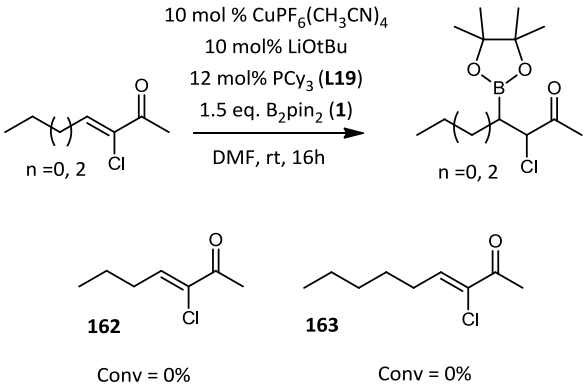
Scheme 3.31. *Borylation of a-chloropnehylbuteneones* ***158****,* ***159*** *and* α*-chlorochalcone* ***161****.*

Interestingly, substrate **160** bearing a *p*-MeO group on the aryl moiety, gave 92% conversion but chemoselectivity completely shifted towards the corresponding α-protonated β-borylated compound **165** (Scheme 3.32).



Scheme 3.32. *Borylation of 3-chloro-4-(4-chlorophenyl)but-3-en-2-one (****160****).*

Finally, substrates **162** and **163**, when submitted to the borylation conditions, gave also no conversion towards any product. In this case we also consider that the reason for such reactivity is the steric bulk produced by the halogen and the long aliphatic chain, which won't allow enough space for the nucleophilic boron to attack on the β-position (Scheme 3.33).



Scheme 3.33. *Borylation of α-chloro-3-hepten-2-one (**162**) and α-chloro-4-nonen-3-one (**166**).*

3.5 Conclusions

In this chapter we have developed and screened different methodologies towards the difunctionalization of α,β-unsaturated carbonyl compounds involving halogenation and borylation chemistry.

We were glad to discover that β-substituted α,β-unsaturated cyclic enones gave better results in terms of chemoselection and regioselection. Optimized conditions and substrate screening concerning different substitution on the β-carbon of the β-substituted cyclic enones, led to a wide array of α-chlorinated β-borylated and α-brominated β-borylated carbonylic compounds with no precedent in the literature, all of them obtained in good to moderate yields.

In comparison, bromination with NBS was less effective than chlorination with NCS. We attribute this fact to the increasing size of the halogen (Br>Cl) thus having an increasing difficulty to interact with the in-situ formed enolate.

In an attempt to increase the substrate scope, we approached the selective α-chlorination of α,β-unsaturated carbonyl compounds, to ultimately synthesize up to ten different α-halogenated substrates using an existing methodology. Several attempts towards the borylation of those newly synthesized compounds finally led to the desired chemoselection for the α-chloro 2-cyclohexen-1-one and α-chloro 3-methyl-2-cyclohexen-1-one. However, the other substrates used gave no conversion to any product. We attribute this fact again to steric interactions of the halogen on the α-position, that won't allow the interaction with LCu-Bpin.

Nevertheless, still a consistent amount of α-halogenated (chlorinated and brominated) β-borylated carbonyl compounds were obtained, being this a pioneering work in the area consisting on the nucleophilic boron addition and in situ electrophilic halogen addition to α,β-unsaturated carbonyl compounds.

3.6 References

[1] E. Drechsel, *Zeitschrift für Biologie* **1986**, *33*, 85.

[2] E. J. Hoekstra, H. De Weerd, E. W. B. De Leer, U. A. Th. Brinkman, *Environmental Science and Technology* **1999**, *33*, 2543.

[3] J. Gan, S. R. Yates, H. D. Ohr, J. J. Sims, *Geophysical Research Letters* **1998**, *25*, 3595.

[4] G. W. Gribble, *Accounts of Chemical Research* **1998**, *31*, 141.

[5] R. S. Berger, *Science* **1972**, *177*, 704.

[6] S. Marumo, H. Hattori, H. Abe, K. Manukata, *Nature* **1968**, *219*, 959.

[7] K. H. Van Pée, *Annual Review of Microbiology* **1996**, *50*, 375.

[8] a) T. Mazzei, A. Novelli, S. Esposito, *J. Chemother.* **2000**, *12*, 53; b) A. T. Bapujee, T. Singh, T. Ahmed, T. Monif, N. Saha, P. L. Sharma, *Eur. J. Drug. Metab. Pharmacokinet.* **2007**, *32*, 205.

[9] N. Price, O. Sartor, T. Hutson, S. Mariani, *Clin. Prostate Cancer* **2005**, *3*, 211.

[10] P. M. Small, H. F. Chambers, *Antimicrob. Agents Chemother* **1990**, *34*, 1227.

[11] M. W. Allsopp, G. Vianello, *Ullmann's Encyclopedia of Industrial Chemistry* **2012**, *28*, 442.

[12] R. E. Doherty, *Environmental Forensics* **2000**, *1*, 69.

[13] a) J. G. Kaplan, J. Kessler, N. Rosenberg, D. Pack, H. H. Schaumburg, *Neurology* **1993**, *43*, 2193; b) R. Tillman, M. Siegel, J. Long, *Pesticide Biochemistry and Physiology* **1973**, *3*, 160; c) D. B. Donald, A. J. Cessna, E. Sverko, N. E. Glozier, *Environ. Health Perspect.* **2007**, *115*, 1183; d) R. Pokorny, *J. Am. Chem. Soc.* **1941**, *63*, 1768.

[14] M. Rossberg, W. Lendle, G. Pfleiderer, A. Tögel, E.-L. Dreher, E. Langer, H. Rassaerts, P. Kleinschmidt, H. Strack, R. Cook, U. Beck, K.-A. Lipper, T. R. Torkelson, E. Löser, K. K. Beutel, T. Mann, *Ullmann's Encyclopedia of Industrial Chemistry* **2006**, *1*, 1.

[15] U.S. Department of State (**2007**). Projected Greenhouse Gas Emissions In: *Fourth Climate Action Report to the UN Framework Convention on Climate Change* . U.S. Department of State, Washington, DC, USA.

[16] G. A. Olah, R. Renner, P. Schilling, Y. K. Mo, *J. Am. Chem. Soc.* **1973**, *95*, 7686.

[17] Y. Halpern, *Isr. J. Chem.* **1975**, *13*, 99.

[18] M. E. Vol'pin, I. S. Akhrem, A. V. Orlinkov,. *New. J. Chem.* **1989**, *13*, 771.

[19] I. S. Akhrem, A. V. Orlinkov, L. V. Afanas'eva, E. I. Mysov, M. E. Vol'pin, *Tetrahedron Letter*s **1995**, *36*, 9365.

[20] J. G. Lee, J. W. Seo, U. C. Yoon, K. –T. Kang, *Bull. Korean. Chem. Soc.* **1995**, *16*, 371.

[21] a) W. Gottardi, *Monatsh. Chem.* **1968**, 99, 815; b) W. D. Brown, A. H. Gouliaev, , *Synthesis* **2002**, 83; c) S. C. Virgil, in *Encyclopedia of Reagents for Organic Synthesis*, ed. By L. A. Paquette, John Wiley & Sons, Chichester, **2001**, pp 1560-1561; d) Z. P. Demko, M. Bartsch, K. B. Sharpless, *Org. Lett.* **2000**, *2*, 2221; e) T. R. Walters, W. W. Zajac Jr., J. M. Woods*, J. Org. Chem.* **1991**, *56*, 316; f) T. Umemoto, R. P. Singh, Y. Xu, N. Saito, *J. Am. Chem. Soc.* **2010**, *132*, 18199.

[22] G. K. S. Parkash, T. Mathew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul, G. A. Olah*, J. Am. Chem. Soc.* **2004**, *126*, 15770.

[23] H. Wu, J. Hynes, *Org. Lett.* **2010**, *12*, 1192.

[24] G. W. Kabalka, E. E. Gooch, K. A. R. Sastry, *J. Nucl. Med*. **1981**, *22*, 908; b) G. W. Kabalka, K. A. R. Sastry, P. G. J. Pagni, *J. Radioanal. Chem.* **1982**, *74*, 315.

[25] a) C. Thiebes, G. K. Surya Parkash, N. A. Petasis, G. A. Olah, *Synlett.* **1998**, 141; b) R. Szumigala, P.N. Devine, D. R. Gauthier Jr., R. P. Volante, *J. Org. Chem.* **2004**, *69*, 566.

[26] a) D. Kalany, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523; b) B. Du, X. Jiang, P. Sun, *J. Org. Chem.* **2013**, *78*, 2786.

[27] M. Sai, S. Matsubara, *Org. Lett.* **2011**, *13*, 4676.

[28] Q. Yan, J. Luo, D. Zhang-Negrerie, H. Li, X. Qi, K. Zhao, *J. Org. Chem.* **2011**, *76*, 8690.

[29] D. W. Tay, I. T. Tsoi, J. C. Er, G. Y. C. Leung, Y. –Y. Yeung, *Org. Lett.* **2013**, *15*, 1310.

[30] L. –X. Shao, M. Shi, *Synlett.* **2006**, 1269.

[31] L. C. Larock, *Comprehenseive Organic Transformations*, 2nd ed. VCH: New York, **1999**.

[32] a) X. –X. Shi, L. –X. Dai, *J. Org. Chem.* **1993**, *58*, 4596; b) S. –F. Cheng, C. –S. Lin, L. K. Liu*, J. Chin. Chem. Soc.* **1997**, *44*, 309; c) M. L. Meketa, Y. R. Mahajan, S. M. Weinreb, *Tetrahedron Lett.* **2005**, *46*, 4749.

[33] a) L. Hintermann, A. Togni, *Helv. Chim. Acta* **2000**, *83*, 2425; b) L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359.

[34] R. Frantz, L. Hintermann, M. Perseghini, D. Broggini, A. Togni, *Org. Lett.* **2003**, *5*, 1709.

[35] D. Yang, Y. –L. Yan, B. Lui, *J. Org. Chem.* **2002**, *67*, 7429.

[36] Y. Zhang, K. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15038.

[37] H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531.

[38] N. Halland, A. Baunton, S. Bachmann, M. Marigo, K. A. Jorgensen, *J. Am. Chem. Soc*. **2004**, *126*, 4790.

[39] a) M. Marigo, S. Bachmann, N. Halland, A. Braunton, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 5507; b) M . Marigo, N. Kumaragurubaran, K. A. Jorgensen, *Chem. Eur. J*. **2004**, *10*, 2133; c) N. Halland, M. A. Lie, A. Kjaersgaard, M. Marigo, B. Schiott, K. A. Jorgensen, *Chem. Eur. J.* **2005**, *11*, 7083.

[40] Y. Mei, P. A. Bentley, J. Du, *Tetrahedron Letters* **2008**, *49*, 3802.

[41] Y. Sato, H. Serizawa, S. Hara, A. Suzuki, *J. Am. Chem. Soc*. **1985**, *107*, 5225.

[42] C. Wang, T. Tobrman, Z. Xu, E. –i. Negishi, *Org. Lett.* **2009**, *11*, 4092.

[43] J. R. Lawson, E. R. Clark, I. A. Cade, S. A. Solomon, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2013**, *52*, 7518.

[44] Q. Jiang, T. Guo, Z. Yhu, *Chem. Cat. Chem.* **2015**, *7*, 660.

[45] N. Ngatimin, Ch. J. Gartshore, J. P. Kindler, S. Naidu, D. W. Lupton, *Tetrahedron Letters* **2009**, *50*, 6008.

I don't know what I may appear to the world, but

To myself I seem to have been only like a boy

Playing on the sea-shore, and diverting myself in

Now and then finding a smoother pebble or a

Prettier shell than ordinary, whilst the great ocean

Of truth lay all undiscovered before me

(Isaac Newton)

4. One-pot synthesis of 2-aryl-1,3-diones through catalytic borylation as a key sequence.

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

4.1 2-aryl-1,3-diones. Background and synthesis.

Intense efforts towards the synthesis of specific type of molecular entities, rely on the utility and importance that molecules have to offer to science and to society in general. 2-Aryl-1,3-diones are not an exception, since this family of compounds have been demonstrated to be excellent and non-toxic herbicides and pesticides in crop fields.

Crop fields such as maize, rice and cereals are indeed attractive for R&D-based crop protection industries[1]. The reason is that an increasing world population requires a more efficient crop production output per area, however, securing and increasing crop yield and quality without compromising the surrounding environment still remains a challenge.

Among other factors, weed infestations remains still nowadays a problem for the final crop yield of the season. Weeds compete with grains for space and natural resources like water, nutrients and light. The loss potential due to weeds in worldwide wheat and barely production was estimated to be 23%, while weed control showed an average crop-protection efficiency of 65% in these two major crops[2].

2-aryl-1,3-diones are nowadays widespread across a range of biologically active pesticides for crop protection[3]. Commercially available examples include Pinoxaden (herbicide), Spirodiclofen (acaricide), and Spirotetramat (insecticide) (Figure 4.1). There are currently more than 200 patents in this chemical area only, demonstrating that every new breakthrough consisting on the synthesis/application of those compounds are of high interest for the industry.

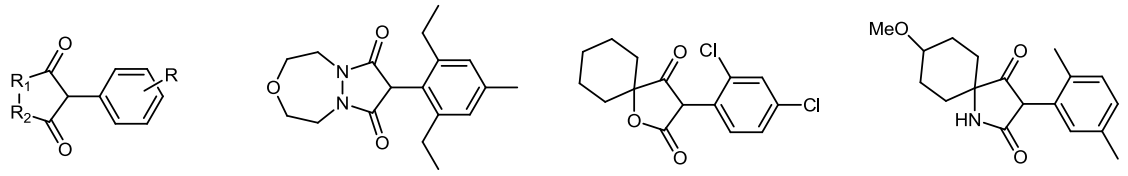
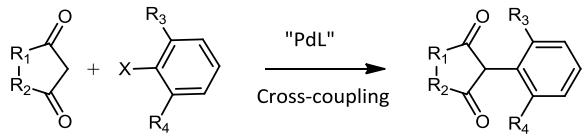


Figure 4.1. *Representative 2-aryl-1,3-diones.*

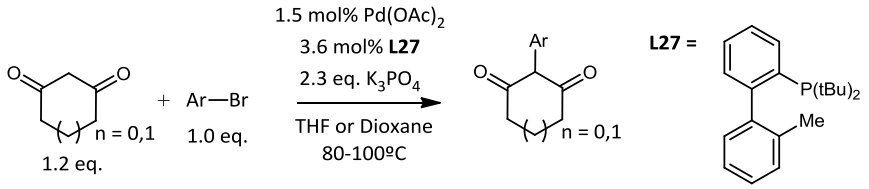
Giving the high importance in this chemical class of compounds, a variety of different methods have been employed for their synthesis. The most favorable approach would be the formation of the dione C-C bond in the final synthetic step by cross-coupling methodology, as this would

allow a convergent synthesis. However, a drawback for this strategy is that almost every biologically active 2-aryl-1,3-dione contain at least one, if not two, ortho substituents on the aryl group, and direct cross-coupling of any cyclic 1,3-dione with an ortho- or diortho-aryl substituted halide or pseudohalide is unprecedented in the literature (Scheme 4.1).



Scheme 4.1. *Unprecedented cross-coupling with ortho substituted aryl halides.*

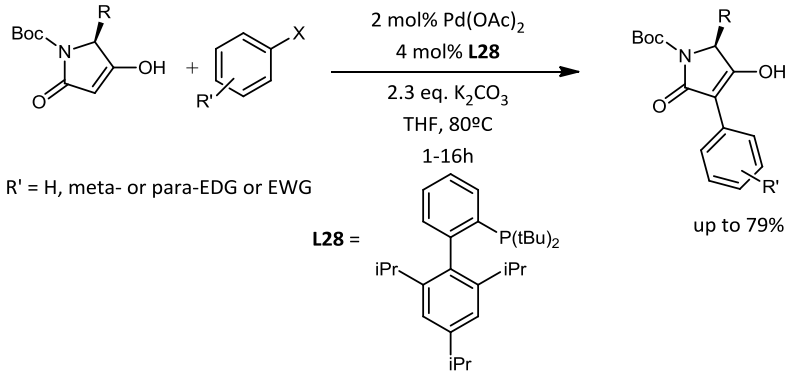
On the other hand, direct cross-coupling of a 1,3-dione with an aryl halide absent of any ortho-substituents have been already reported. Buchwald et al.[4] reported an efficient α-arylation of cyclic and acyclic 1,3-dicarbonylic compounds using as optimized conditions a particular type of catalytic system using $Pd(OAc)_2$/ **L27** providing high yields of the resulting coupled compounds (Scheme 4.2).



Ar-Br = 1-bromo-3,5-dimethylbenzene
1-bromo-4-tertbutylbenzene
methyl-3-bromobenzoate

Scheme 4.2. *α-arylation of 1,3-dicarbonyl compounds through catalytic cross-coupling.*

Also, Tanner et al.[5] reported a mild palladium-catalyzed α-arylation of tetramic acids, obtaining conversions higher than 95% in some cases within only 1h. The nature of the substituents on the aryl-halide was not important towards the reaction outcome. However, again the aryl ring-substitution was limiting, since only meta- and para-substituted aryl-halides were successfully coupled (Scheme 4.3).



Scheme 4.3. *α-arylation of tetramic acids by catalytic cross-coupling.*

Since direct cross-coupling is not yet an available methodology for the synthesis of o-substituted 2-aryl-1,3-diones, other methodologies have been applied and sought towards the synthesis of ortho- and diortho-substituted 2-aryl-1,3-diones. For example the synthesis of Pinoxaden and its derivatives has been reported by Syngenta[1]. The dione part along with the aryl group are built together, whereas the hydrazine part is built in parallel. Both fragments are then coupled to form the desired dione(Figure 4.2).

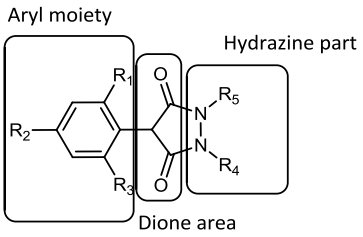
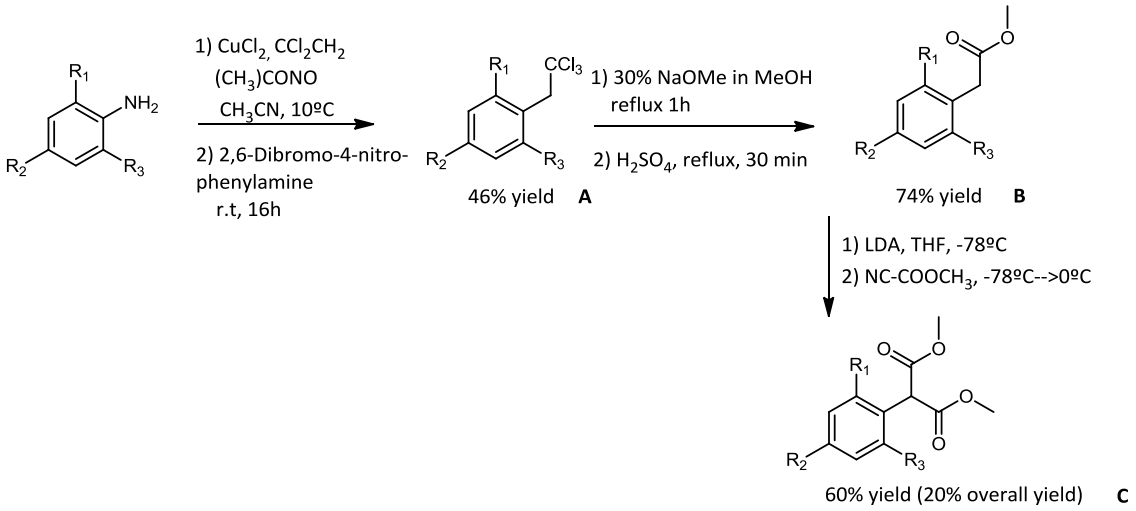


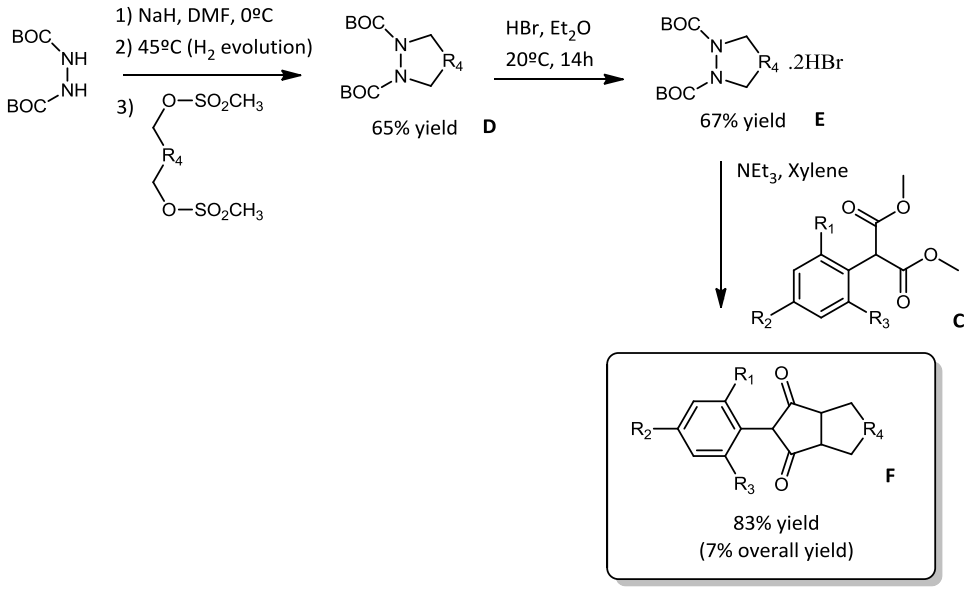
Figure 4.2. *Key fragments of Pinoxaden-based dione.*

As a model for aryl-dione synthesis, it has been used 2,4,6-trisubstituted aniline, to perform a copper catalyzed transformation towards a (trichloromethyl-propane)-2,4,6-trisubstituted aryl **A** in moderate yield. Secondly, basic treatment of **A** with NaOMe under reflux and further acid treatment would generate the corresponding methyl propionate **B** in high yield. As a final step, the aryl-substituted methyl propionate would be treated with in-situ generated LDA at -78ºC upon the addition of methyl cyanoformate, to generate the bis(methylpropionate)-2,4,6-trisubstituted-aryl fragment **C** in good yield. The overall yield of the fragment lies around 20% (Scheme 4.4).



Scheme 4.4. *Synthesis of aryl-moiety of Pinoxaden-based dione.*

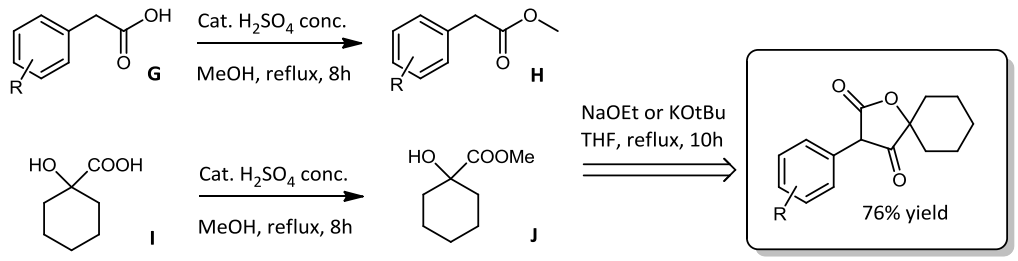
In parallel, and for the synthesis of the azide ring, 1,2-bis-BOC-hydrazine was treated with NaH in DMF at 0ºC. Right after, the reaction vessel was heated at 45ºC to let hydrogen evolution (very carfully because multigram scale synthesis might generate a significant quantity of hydrogen which is explosive). Finally, a 2,5-bis(methanesulfonyloxymethyl) derivative was added at 0ºC, then heated for 7h to achieve benzyloxy-[1,2]diazepane ring **D** in good yield. Treatment of **D** with HBr at r.t for 20h led to the corresponding bromhydric acid conjugated derivative **E** in 67% yield. Finally, fragment **C** and fragment **E** were coupled using a solution of NEt_3 in Xylene, to give the final 2-aryl-1,3-dione **F** in excellent yield. The overall isolated yield however is around 7% of the desired product (Scheme 4.5).



Scheme 4.20. *Hydrazine part synthesis and final synthesis of Pinoxaden.*

Alternatively, the synthesis of Spirodiclofen[6] and its derivatives has been covered by different groups[7,8].

The esterification reaction of 2-arylacetic acid **G** produces methyl 2-arylacetate **H** which was not necessary to purify for further reactivity. In parallel, a second esterification of 1-hydroxycyclohexanecarboxylic acid **I**, to obtain the corresponding methyl 1-hydroxycyclohexanecarboxylate **J**, didn't require purification either. Both reaction crudes having compounds **H** and **J** were used to conveniently obtain the corresponding cyclization product using a modified one-pot cyclization method developed by Thierry Le Gall et al.[9] using NaOEt or KOtBu in THF and under reflux for 10h, to finally obtain Spirodiclofen-based diones in excellent isolated yield (76%) (Scheme 4.6).



Scheme 4.6. *Synthesis of Spirodiclofen-based dione.*

The synthesis of the most structurally simple 2-arylcyclopentane-1,3-diones with ortho- and diortho-substitution on the aryl moiety (Figure 4.3), it was published for the first time 35 years ago. The authors of this patent[10] were succesfull on synthesizing those compounds with acaricidal an herbicidal activity to certain extent. The importance of the synthesis of such compounds also relies on the fact that very small dosages are needed to be pesticidally effective in some cases. Nevertheless, the synthesis itself involves utilization of fairly dangerous chemicals when used in multi-gram scale.

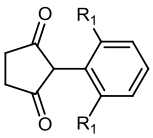
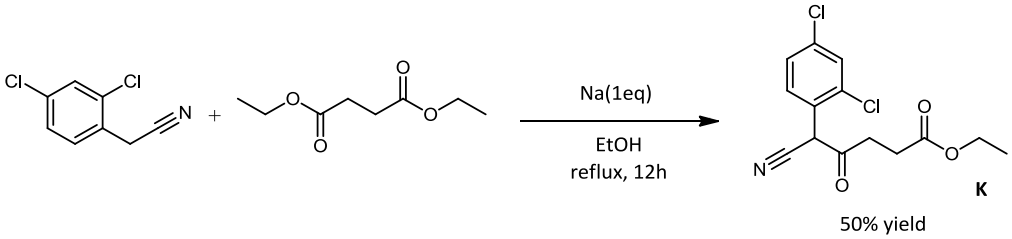


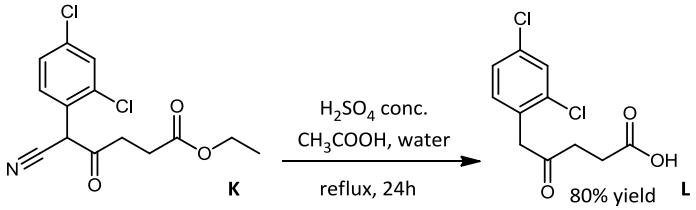
Figure 4.3. *2-arylcyclopentane-1,3-dione.*

To give an example, the synthesis of 2-(2',4'-dichlorophenyl)-1,3-cyclopentanedione can be prepared in four consecutive steps. The first step of the synthesis involves reactivity with 2,4-dichlorobenzyl cyanide and diethyl succinate. Before the addition of the reactants to the reaction vessel, the mentioned can be charged with destilled ethanol, followed by the addition of 1 eq. of Na. The flask is then heated until all sodium dissolved. The temperature is raised to the reflux point, and that's where 2,4-dichlorobenzyl cyanide and diethyl succinate are added. The whole reaction mixture is refluxed under inhert atmosphere for 12h, until 2/3 of the ethanol is destilled off, then more ethanol is added and the refluxing is continued for an additional 2h. After work-up, 5-(2',4'-dichlorophenyl)-5-cyano-4-ketopentanoate **K** was obtained in a 50% I.Y (Scheme 4.7).



Scheme 4.7. *Synthesis of 5-(2',4'-dichlorophenyl)-5-cyano-4-ketopentanoate.*

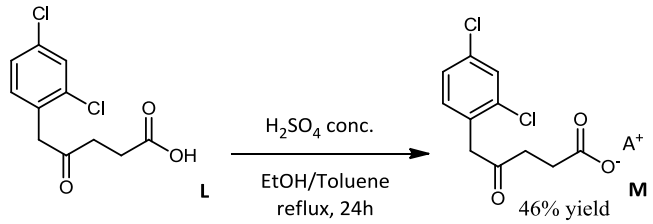
The second step of the synthesis, involves decyanation and reverse esterification to obtain the corresponding pentanoic acid. The procedure consists on adding several mL of concentrated H_2SO_4, water, and glacial acetic acid and intermediate **K**. The whole stirring solution is brought to reflux for 24h. After work-up, 5-(2',4'-dichlorophenyl)-4-ketopentanoic acid **L** was obtained in 80% yield (Scheme 4.8).



Scheme 4.8. *Synthesis of 5-(2',4'-dichlorophenyl)-4-ketopentanoic acid.*

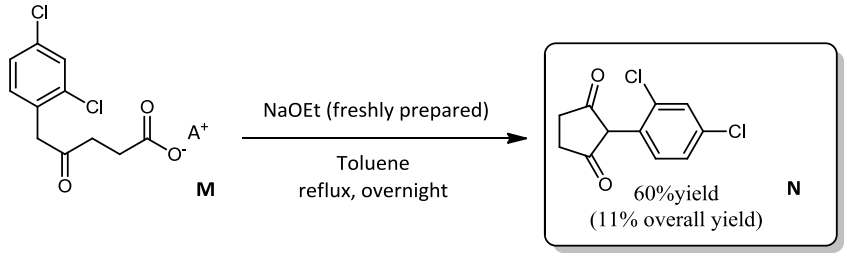
The third step, involves the synthesis of the corresponding pentanoate from the pentanoic acid. The pentanoic acid derivative was dissolved in a mixture EtOH/toluene. Then, concentrated sulfuric acid is added, and the whole mixture was stirred and refluxed through a

Soxhlet extractor containing 3A M.S. for 24h. After the corresponding work-up, 5-(2',4'-dichlorophenyl)-4-ketopentanoate **M** was obtained in a 46% yield (Scheme 4.9).



Scheme 4.9. *Synthesis of 5-(2',4'-dichlorophenyl)-4-ketopentanoate.*

The final step of the synthesis involves a base-promoted cyclization of the pentanoate. The methodology reported by the authors consists on preparing fresh NaOEt from Na and EtOH using a Dean-stark apparatus. Once all EtOH is destilled off and the powder of the NaOEt is lying down the reaction vessel, toluene is added, and finally the corresponding pentanoate is also added. The whole solution is refluxed overnight. After the corresponding work-up, 2-(2',4'-dichlorophenyl)-1,3-cyclopentanedione **N** was obtained in a 60% yield. The overall yield of the 4 steps is 11% (Scheme 4.10).



Scheme 4.10. *Synthesis of 2-(2',4'-dichlorophenyl)-1,3-cyclopentanedione.*

4.2 Objectives of work

Taking into consideration the current interest to find straightforward synthetic methods to prepare α-aryl-1,3-diones, we planned to design a concise protocol based on the catalytic borylation reaction.

The particular objectives are:

1.- Simplify the number of synthetic steps.

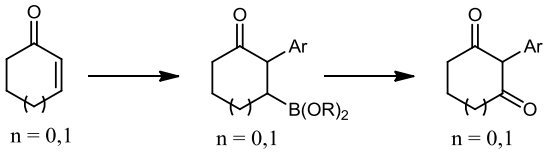
2.- Reduce the purification of chemical intermediates.

3.- Make the whole process greener to avoid highly toxic and dangerous chemicals.

4.- Provide a new global synthesis with isolated yields higher than current methodologies that open a new prespective in the scale up.

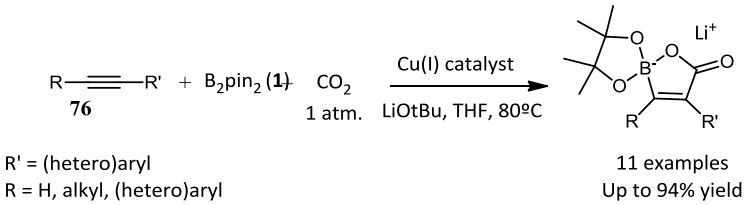
Work Hypothesis:

We envisage a methodology based on α-arylation / β-borylation of α,β-unsaturated cyclic ketones, with concomitant oxidative work-up.



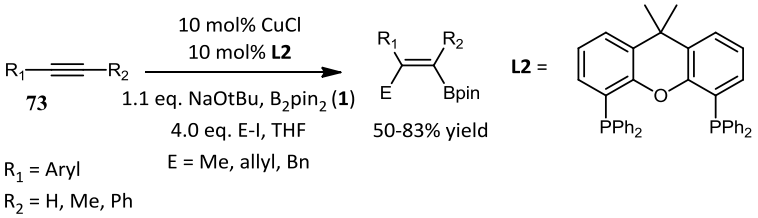
4.3 Results and discussion

Initially, we were interested to look for efficient carboboration protocols. In the literature there are few examples involving carboboration of unsaturated double and triple bonds. Hou et al.[11] reported the boracarboxylation of alkynes (diaryl alkynes, aryl/alkyl alkynes, and phenyl acetylene) with a diboron reagent and carbon dioxide, affording α,β-unsaturated β-boralactones in a regio- and stereoselective manner (Scheme 4.11).



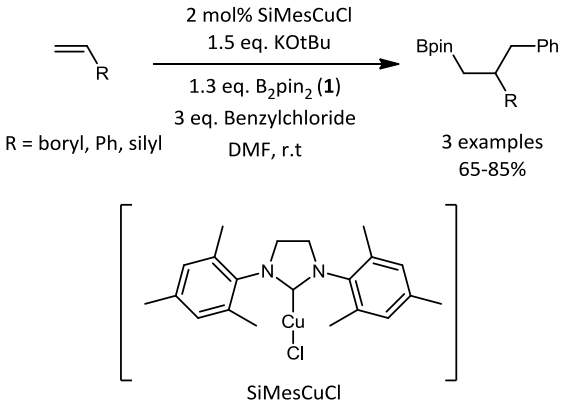
Scheme 4.11. *Boracarboxylation of alkynes.*

Similar work reported by Tortosa et al.[12] shows us the first formal carboboration of alkynes in which a C-B bond and a C-C bond are created in a single catalytic cycle. The reaction proceeds with high regio- and *syn*-stereoselectivity to form tri- and tetrasubstituted vinyl boronic esters. Subsequent cross-coupling offers the possibility to give access to highly substituted alkenes (Scheme 4.12).



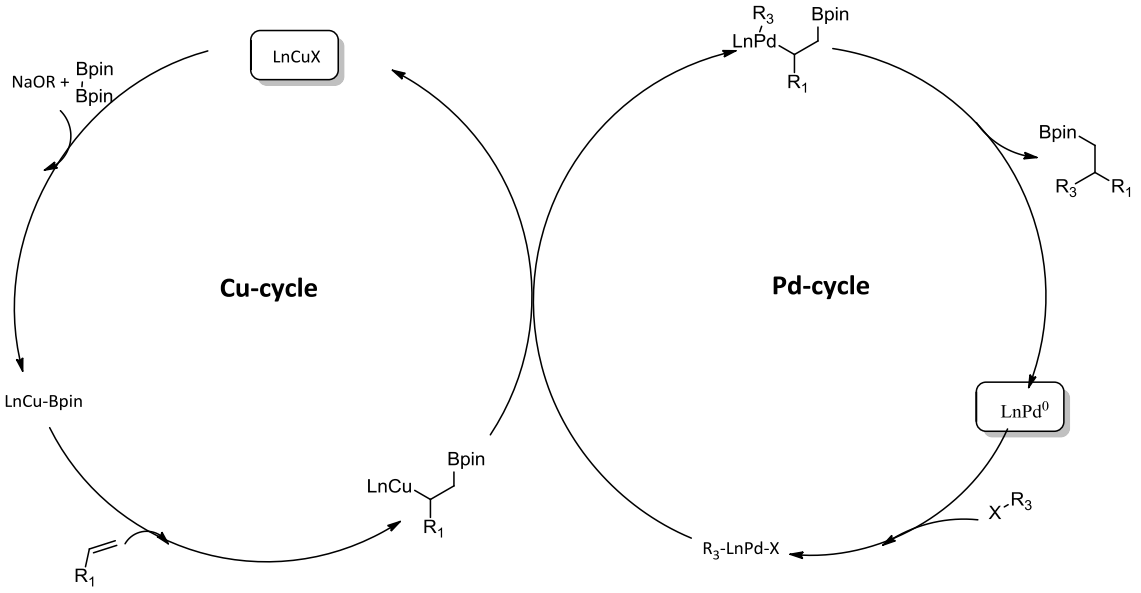
Scheme 4.12. *Cu-catalyzed carboboration of alkynes.*

Also, carboboration of alkenes was reported by Takaky et al.[13] where they address the first Cu-catalyzed carboboration of alkenes using B_2pin_2 (**1**) as the boron source and benzyl-chloride as the electrophile, leading to the formation of multisubstituted boryl alkanes via regioselective C-B and C-C bond formation (Scheme 4.13). However the scope seems to be limited, since only benzylchloride was successfully coupled.



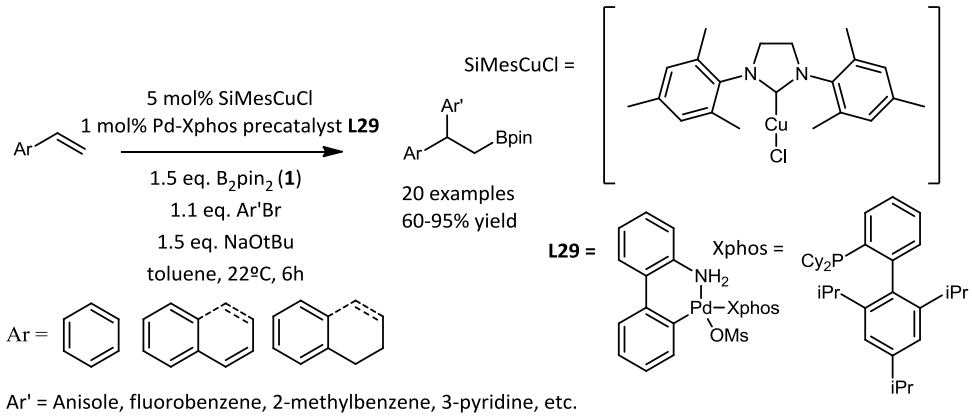
Scheme 4.13. *Cu-catalyzed carboboration of alkenes.*

Another methodology developed by Brown et al.[14] details a very practical example concerning carboboration of alkenes, where the nature of the alkene itself neither the aryl group seem to be a limitation. In this case, a synergistic Pd/Cu catalytic system generates a Cu-based nucleophile from simple alkenes and diboron reagents, followed by Pd-catalyzed cross-coupling. The catalytic cycle consists on an in-situ formation of a Cu-Csp^3 by the reaction of Cu-Bpin active species with an alkene. Subsequent reaction with a [PdL_nArX], generated by oxidative addition of a [Pd^0L_n], provides a new Pd-Csp^3 complex, which upon reductive elimination, generates the product (Scheme 4.14).



Scheme 4.14. *Mechanism for synergistic catalysis.*

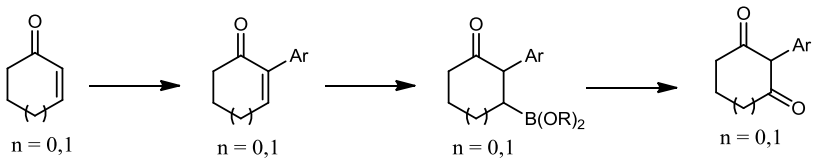
Upon optimized reaction conditions, Brown et al.[14] demonstrated that several examples involving aryl/vinyl bromides, and substrates such as styrene, 2-vinylnaphthalene and 1,2-dihydronaphthalene gave excellent yields and regioselectivities, where the C-B bond is formed on the external position of the terminal alkenes, and the new C-C bond on the internal position (Scheme 4.15).



Scheme 4.15. *Pd/Cu catalyzed carboboration of alkenes.*

Encouraged by the results reported by Brown et al.[14], we wanted to screen if the mentioned catalysts would yield us some conversion towards α-arylated β-borylated cycloenones. However, all the attempts failed. Probably, the enolate formed next to the carbonyl group might be to reactive and therefore ends up as α-protonated β-borylated cycloenones.

At that point, we wanted to approach the synthesis from a different perspective. We thought that sequential Pd-cross coupling on the α-position of an α,β-unsaturated ketone, followed by catalytic borylation, would yield the desired α-arylated, β-borylated intermediate, which is the key intermediate to finally obtain the 1,3-diones (Scheme 4.16).



Scheme 4.16. *Sequential Pd-cross coupling /Cu-borylation of cycloenones.*

In the context of suitable cross-coupling Suzuki-Miyaura reactions[15], we found a protocol by Felpin et al.[16] that describes the first Suzuki-Miyaura cross-coupling of 2-iodocycloenones

with arylboronic acids catalyzed by 10% Pd/C. This alternative is indeed interesting because the Pd/C catalyst is air stable, and the whole reaction can be performed in a mixture of DME/H_2O in open air atmosphere and under very mild conditions depending on the arylboronic acid used. Also, since the palladium catalyst forms an heterogeneous system can be recycled up to 5 times. We consider this alternative a very feasible approach to start our synthesis, since the conditions used are fairly green and potentially useful for industry because of their simplicity.

To prepare the 2-iodocycloenones from α,β-unsaturated cycloenones, we followed a previously reported method[17] and in our hands similar values of conversion and isolated yields for both cyclohexenone and cyclopentenone were obtained (Table 4.1).

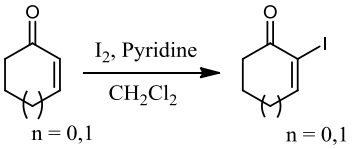
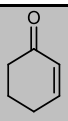
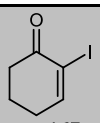


Table 4.1. *Synthesis of 2-iodocycloenones.*

Entry	Substrate	Product	Conversion[b]	I.Y.
1[a]		 **167**	83%	76%
2[a]		 **168**	77%	64%

[a]*Standard conditions*: Cyclic enone (15 mmol) and 1/5 pyridine-CH_2Cl_2 (17.5 mL), a solution of I_2 (1.5 eq, 15 mmol) added over 1h. The mixture was stirred for an additional 14h, quenched with 50 mL of citric acid (6% aqueous solution), and extracted with CH_2Cl_2. [b]Conversion determined by ^{1}H NMR spectroscopy and GC analysis.

We planned the next step for the Pd-cross coupling of 2-iodocycloenones **167** and **168** and arylboronic acids **109**. Using the same conditions described for the coupling using Pd/C catalyst[17], conversions were quantitative and isolated yields for 2-aryl cycloenones were comparable to previously reported synthesis (Table 4.2 and Table 4.3). We were delighted to observe, that compounds bearing ortho-substitution on the aryl group (**172**-**176** and **180**-**188**) were easily coupled and isolated. Interestingly, compounds **175**, **176**, **180**, **181**, **183**, **184**, **185**, **186**, **187** and **188** were prepared for the first time in this work.

Also, we wanted to screen if a di-ortho substituted arylboronic acid, in that case mesitylboronic acid, would perform the cross coupling just like the mono-substituted boronic acids did. That was not the case, and to achieve conversion, we had to adapt an already existing methodology reported by Buchwald et al[18] in the preparation of extremely hindered biaryls, but using a very efficient Pd-Xphos precatalyst **L30** used by Brown et al. in alkene carboboration protocols[14]. Carrying the reaction in toluene and working at 110ºC, we obtained **188** up to 95% conversion and 30% isolated yield of di-ortho substituted 2-aryl cyclopentenone. To the best of our knowledge, this is the first time that a di-ortho substituted 2-aryl cyclopentenone has been synthesized.

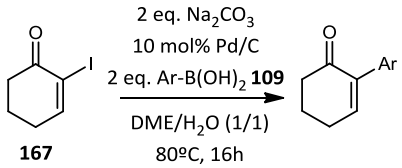
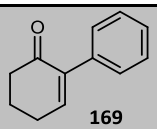
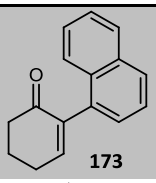
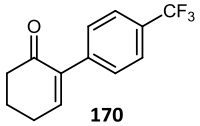
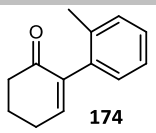
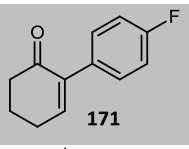
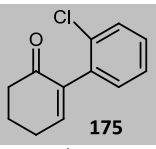
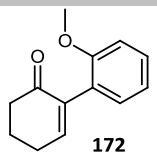
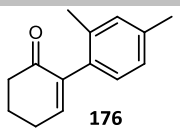


Table 4.2. *Synthesis of 2-aryl cyclohexenones.*

Entry	Product	Conv(%)[b]	I.Y.(%)	Entry	Product	Conv(%)[b]	I.Y.(%)
1[a]	 **169**	84	47	**5**[a]	 **173**	95	52
2[a]	 **170**	97	52	**6**[a]	 **174**	99	69
3[a]	 **171**	73	51	**7**[a]	 **175**	99	56
4[a]	 **172**	86	44	**8**[a]	 **176**	99	82

[a]Standard conditions: α-iodoenone **167** (1 mmol), DME(4mL), H_2O (4 mL), Na_2CO_3 (2 mmol), Aryl-$B(OH)_2$ **109** (2 mmol), 10% Pd/C, 80ºC, 16h. [b]Conversion determined by ^{1}H NMR spectroscopy and GC analysis.

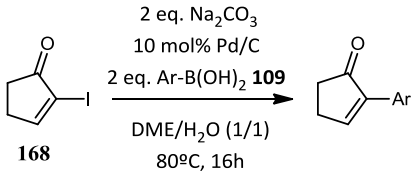
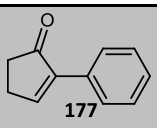
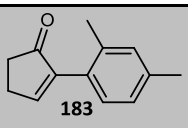
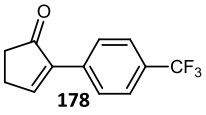
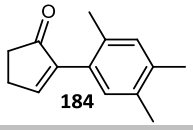
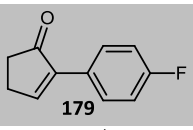
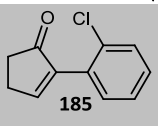
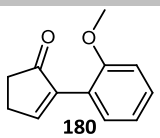
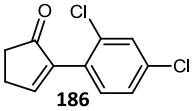
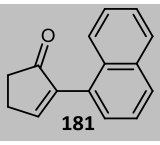
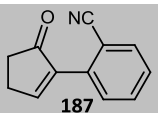
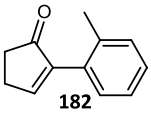
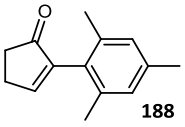


Table 4.4. *Synthesis of 2-aryl cyclopentenones.*

Entry	Product	Conv(%)[c]	I.Y.(%)	Entry	Product	Conv(%)[c]	I.Y.(%)
1[a]	 **177**	99	51	**7**[a]	 **183**	99	59
2[a]	 **178**	99	24	**8**[a]	 **184**	99	65
3[a]	 **179**	99	62	**9**[a]	 **185**	99	28
4[a]	 **180**	99	36	**10**[a]	 **186**	99	48
5[a]	 **181**	99	51	**11**[a]	 **187**	99	26
6[b]	 **182**	99	23	**12**[b]	 **188**	95	30

[a]Standard conditions: α-iodoenone **168** (1 mmol), DME(4mL), H_2O (4 mL), Na_2CO_3 (2 mmol), Aryl-$B(OH)_2$ **109** (2 mmol), 10% Pd/C, 80ºC, 16h. [b]Pd-Xphos G3 (0.025 mmol), K_3PO_4 (1.5 mmol), mesitylboronic acid (0.55 mmol) and α-iodoenone (0.5 mmol), Toluene (4 mL), 110ºC, 16h. [c]Conversion determined by ^{1}H NMR spectroscopy and GC analysis.

Encouraged by these results, we next focused on the Cu-mediated β-boration of 2-aryl cycloenones **169**-**188**, as an efficient way to introduce the boryl moiety from accessible bis(pinacolato)diboron (B_2pin_2). Catalytic borylation approaches are attracting significant interest in industry for the high reactivity and environmental friendly character of the boron reagents and organoboron intermediates[19]. The conjugate borylation of α,β-unsaturated acceptors involves a nucleophilic attack of a boryl moiety to the β-carbon[20]. Copper alkoxyde (formed in situ from CuCl and NaOR) reacts with B_2pin_2 (**1**) to deliver the boryl-copper species (Cu-Bpin), as an active nucleophilic boron source in the β-boration reaction[21].

We conducted the Cu-catalyzed β-boration of 2-aryl cycloenones, in the presence of PCy_3 as the copper ligand and the β-borylation addition was quantitative in all cases, with high values of diaestereomeric ratio on the *trans* isomer (Table 4.4 and Table 4.5). The product 2-phenyl-3-pinacolboryl cycohexanone **169b** was easily prepared and isolated as a single *trans*-diaestereomer, however, the analogous 5-membered ring bearing a phenyl group **177b**, was obtained in a diaestereomeric mixture *trans*/*cis* (70/30). On the case of the cyclopentenones, slightly better diastereoselection on *trans* 2-aryl-3-pinacolboryl cyclopentanone was observed in the β-boration of 2-aryl-cyclopent-2-enones **179b**, **183b**, **184b**, and **185b**. Interestingly, only one diastereoisomer was formed for the ortho-substituted aryl-cyclopent-2-enones, such as **178b**, **180b**, **182b**, **186b** and **187b** (Table 4.6) with special emphasis on the formation of *trans*-2-(naphthalen-1-yl)-3-pinacolboryl cyclopentanone (**181b**) with 86% of isolated yield on one single isomer (Table 4.5).

2-Aryl-3-pinacolboryl cyclohexanones were obtained and isolated mainly as the *trans* diaestereomer, except for the cases **172b** and **176b,** where diaestereomeric mixtures close to *trans*/*cis* (50/50) were obtained (Table 4.4). However, this method had the limitation on the β-boration of 2-mesitylcyclopent-2-enone **188** since no C-B bond could be formed under the same reaction conditions. We also tried to conduct the reaction in a metal free context[22] heating the reaction at 70ºC, in order to circumvent the sterical hindrance around the copper. Even in the organocatalytic framework, the reaction did not proceed towards the desired product, probably due to the difficulty to bring together the Lewis acid-base adduct [MeO^- →Bpin-Bpin] to the Cβ with a mesityl group in Cα.

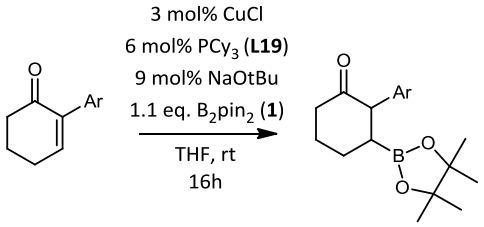
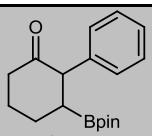
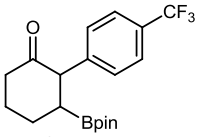
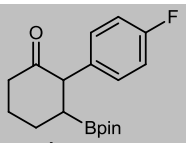
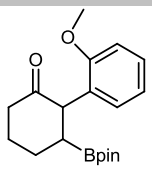
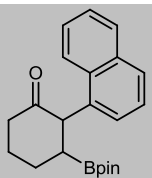
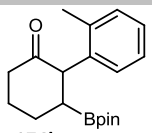
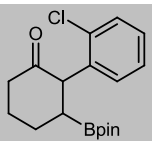
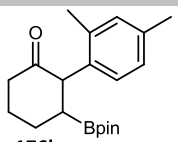
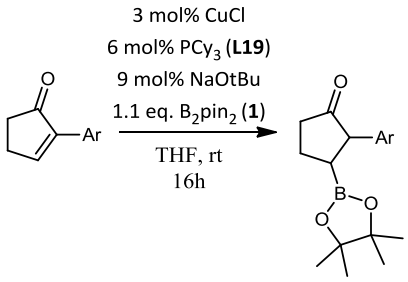


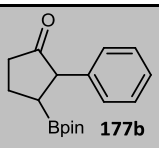
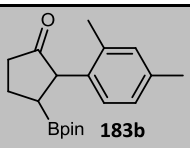
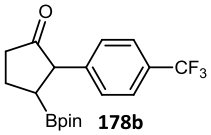
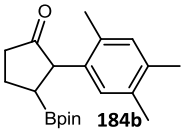
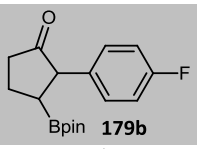
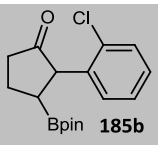
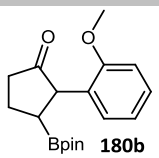
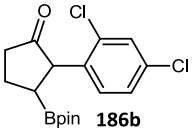
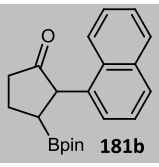
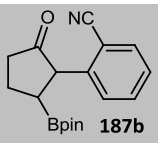
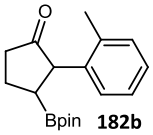
Table 4.4. *Synthesis of β-borylated α-arylated cyclohexanones.*

Entry	Product	Conv(%)[b]	I.Y.(%)	*trans/ cis*[c]
1[a]	 **169b**	96	63	99/ 1
2[a]	 **170b**	99	64	99/ 1
3[a]	 **171b**	96	70	99/ 1
4[a]	 **172b**	99	47	50/ 50
5[a]	 **173b**	99	76	99/ 1
6[a]	 **174b**	99	66	99/ 1
7[a]	 **175b**	99	21	99/ 1
8[a]	 **176b**	99	67	63/ 37

[a]Standard conditions: CuCl (3 mol%), PCy_3 (**L19**) (6 mol%), NaOtBu (9 mol%), B_2pin_2 (**1**) (1.1 eq.), THF (2 mL), MeOH (2.5 eq.) aryl-ketone (0.25 mmol), rt, 16h. [b]Conversion determined by ^{1}H NMR spectroscopy and GC analysis. [c]Diaestereoselection determined by ^{1}H NMR spectroscopy.

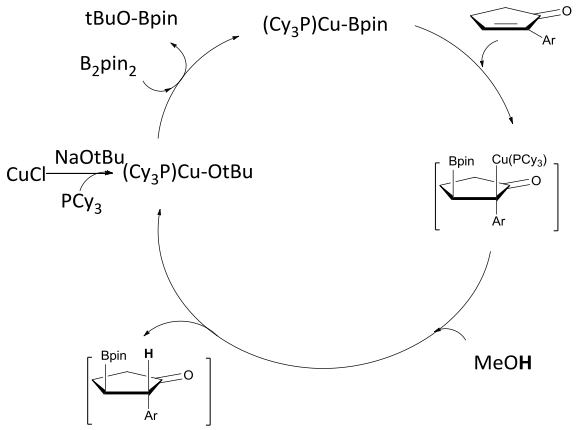


Scheme 4.5. *Synthesis of β-borylated α-arylated cyclopentanones.*

Entry	Product	Conv(%)[b]	I.Y.(%)	*trans/ cis*[c]	Entry	Product	Conv(%)[b]	I.Y.(%)	*trans/ cis*[c]
1[a]	 **177b**	99	51	70/ 30	**7**[a]	 **183b**	99	65	80/ 20
2[a]	 **178b**	99	70	99/ 1	**8**[a]	 **184b**	99	66	86/ 14
3[a]	 **179b**	99	25	83/ 17	**9**[a]	 **185b**	99	53	83/ 17
4[a]	 **180b**	99	70	99/ 1	**10**[a]	 **186b**	99	48	99/ 1
5[a]	 **181b**	99	86	99/ 1	**11**[a]	 **187b**	99	62	99/ 1
6[a]	 **182b**	99	49	99/ 1					

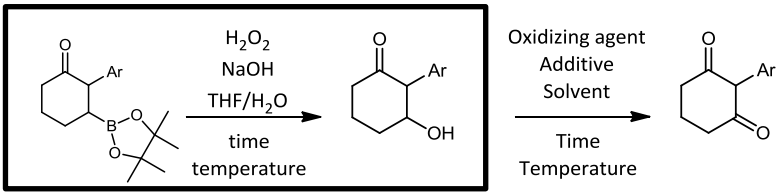
[a]Standard conditions: CuCl (3 mol%), PCy_3 (**L20**) (6 mol%), NaOtBu (9 mol%), B_2pin_2 (**1**) (1.1 eq.), THF (2 mL), MeOH (2.5 eq.) aryl-ketone (0.25 mmol), rt, 16h. [b]Conversion determined by ^{1}H NMR spectroscopy and GC analysis. [c]Diaestereoselection determined by ^{1}H NMR spectroscopy.

Scheme 4.17 illustrates the catalytic cycle and the favored trend to generate *trans* diastereoisomers, on the 2-aryl cyclopentenones. Interestingly, the β-borated products **169b**-**187b** were prepared for the first time in this work.



Scheme 4.17. *Suggested catalytic cycle for the β-boration of 2-aryl cycloenones.*

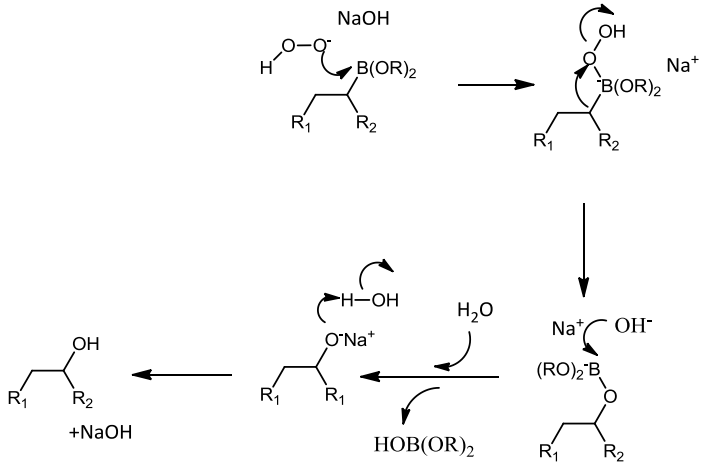
Once the whole set of α-aryl β-boryl cycloenones was successfully prepared, we next focused in the oxidation of the C-B bond, in order to obtain the corresponding diones. The C-B bonds are well known for their versatility in organic synthesis, since their transformation into a wide variety of functional groups has been well studied[23]. Among their most common transformations, the most typical one is the C-B to C-OH, either using an aqueous mixture of H_2O_2/NaOH, or milder conditions using $NaBO_4.4H_2O$[24]. However, to the best of our knowledge, the direct oxidation of C-B to C=O has not been reported. Therefore, we first envisaged a one pot, two steps oxidation protocol from C-B to C-OH followed by C-OH to C=O, in order to obtain the dione in the goal (Scheme 4.18).



Scheme 4.18. *One-pot oxidation steps.*

The intrinsic oxidation of C-B bonds using H_2O_2/NaOH is well known as well as their mechanism. In that case, when the mixture is added into the reaction media, NaOH

deprotonates the hydrogen peroxide, which generates the conjugate base of hydrogen peroxide (acid-base reaction). The resulting NaOOH then attacks the boron's empty π-orbital, and this sets up the following migration step, where the carbon-boron bond migrates to the oxygen bound to boron, thus breaking the weak oxygen-oxygen bond. The OH expelled comes back to form a bond on the boron, which would then eliminate as a $HOB(OR)_3$, leaving the deprotonated alcohol, which protonates because of the water present in the media to generate the corresponding alcohol (Scheme 4.19).



Scheme 4.19. *Mechanism for C-B bond oxidation using H_2O_2/NaOH.*

When the compound **169b** was oxidized in the presence of H_2O_2/NaOH, we observed the α-arylated cyclohexanone **169** as the unique product, probably as a consequence of the basic conditions needed for the oxidation, leading to an elimination type of reaction of the acidic H in Cα (Table 4.6 entry 1). Under similar reaction conditions (rt, 4h) the reagent $NaBO_3.H_2O$ was used instead, but again the α-arylated cyclohexenone was formed (Table 4.6, entry 2). Interestingly, the use of H_2O_2/NaOH in a mixture THF/Et_2O resulted in a 40% formation of the desired 3-hydroxy-2-aryl-cyclohexanone **169c** (Table 4.7 entry 3). Shortening the reaction time down to 30 minutes, led to the quantitative conversion towards the alcohol with a <10% elimination (Table 4.6 entry 5). When we extended this protocol to the borylated cyclohexanone **172b**, the amount of hydroxylated product was 90%.

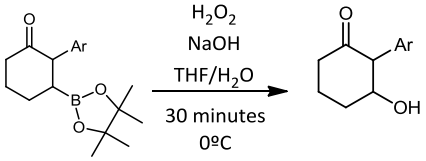
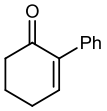
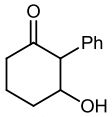


Table 4.6. *Optimization of C-B oxidation conditions.*

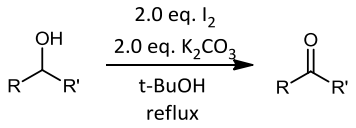
Entry	Oxidant	Solvent	T(ºC)	t(h)	 **169**	 **169c**
1[a]	H_2O_2(32%)/NaOH	THF	rt	4h	100[c]	
2[b]	$NaBO_3.H_2O$(3 eq)	THF	rt	4h	100[c]	
3[a]	H_2O_2(32%)/NaOH	THF/Et_2O	0ºC	6h	60[c]	40[c]
4[a]	H_2O_2(32%)/NaOH	THF/Et_2O	0ºC	1h	16[c]	84[c]
5[a]	H_2O_2(32%)/NaOH	THF/ET_2O	0ºC	30min	7[c]	93[c][90[d]]

[a]Standard conditions: 2N NaOH/ 32%H_2O_2 (2:1 v/v), THF/Et_2O (1:1 v/v); [b]Standard conditions: $NaBO_3.H_2O$ (3 eq.) in THF; [c]Conversion (%) determined by ^{1}H NMR specgtroscopy; [d]Isolated yield (%)

In order to perform the last oxidation from the alcohol to the ketone, we considered different scenarios.

There are indeed several reported methodologies that would allow the transformation of C-OH to C=O, but since our goal would be to perform this reaction using the less toxic/milder conditions possible, we started by using a methodology reported by Togo et al.[25], based with the reactivity of molecular iodine and a base.

Molecular iodine is a mild, cheap and easily available reagent, moreover it is usefull because of its solid form, in comparison to molecular chlorine and bromine. The authors suggest an oxidation of alcohols to the corresponding esters and ketones using molecular iodine and K_2CO_3 in protic polar solvents. In the case of the ketones, they report successful conversion of benzylic and aliphatic secondary alcohols, cyclic and acyclic alcohols and also with a different variety of other functional groups within their molecular structure. Therefore, we thought this might be an interesting approach towards the oxidation of C-OH to C=O in our case, because of the simplicity and the mild reaction conditions needed for the transformation (Scheme 4.20).

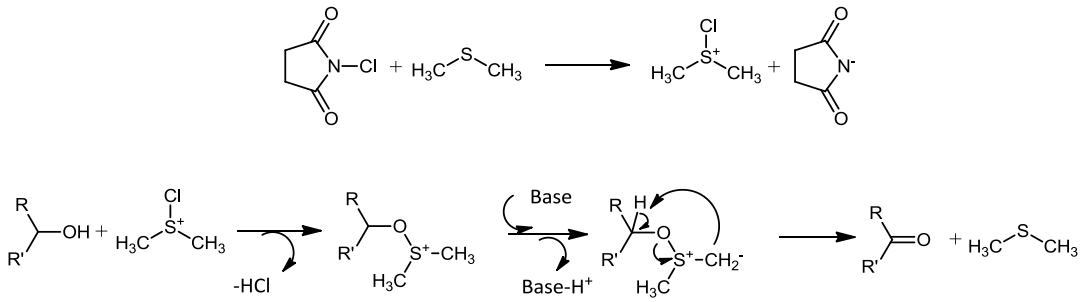


Scheme 4.20. *Oxidation of secondary alcohols to ketones using I_2/K_2CO_3.*

We soon realized however, that applying the same conditions used for the authors, we obtained complete alcohol elimination, obtaining exclusively the 2-arylcyclohexenone. We suggest that the external base used in this procedure (K_2CO_3) is a drawback because the pronounced acidity of the proton on the Cα position.

After this attempt, we consider to look for an alternative method for oxidation of C-OH. That would be the case of the well-known Corey-Kim oxidation methodology.

The Corey-Kim oxidation allows the synthesis of aldehydes and ketones from primary alcohols and secondary alcohols, respectively[26]. Mechanistically, a dimethylchlorosulphonium ion is generated in situ from N-chlorosuccinimide (NCS) and dimethylsulfide (DMS). The dimethylsulphonium ion generated in situ coordinates to the alcohol, then, a base such as NEt_3 is added at -25ºC and after 5 minutes, the reaction is quenched, and the newly formed carbonylic group is obtained in high yields (Scheme 4.21). This procedure looked interesting and promising for us because even though we use an external base that could potentially deprotonate on the Cα position, we have to work at very low temperatures (-25ºC) and for very short reaction times (5 min), so presumably avoiding undesired elimination pathways.



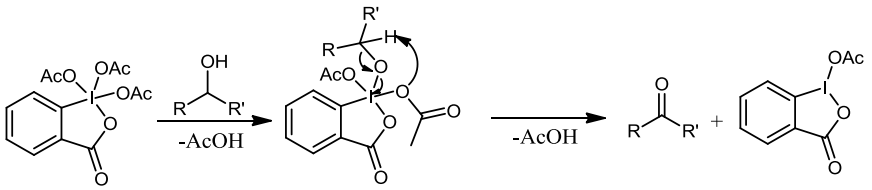
Scheme 4.21. *Proposed mechanism for the Corey-Kim oxidation.*

Unfortunately, despite the fact that the reaction was quenched 5 minutes after the addition of the base at -25ºC, 85% of elimination and 15% of alcohol were remaining in the reaction crude.

Working at low temperatures and short reaction times doesn't favor the formation of the dione, and still the elimination pathway is much favored.

At that point, we considered to look for oxidation methodologies that do not involve any external base for their proceeding, since so far it seems that the external base will preferentially coordinate to the H in Cα leading finally to the elimination product.

For this purpose, we screened conditions for the Dess-Martin oxidation. Dess-Martin periodinane (DMP), a hypervalent iodine compound, offer selective and very mild conditions for oxidation of alcohols to aldehydes and ketones[27]. The oxidation is performed generally in dichloromethane or chloroform at room temperature, and it is usually complete within 0.5-2 hours, and the products are easily separated from the byproduct. Mechanistically, one of the acetates interacts with the alcohol and generates AcOH. Then, a rearrangement takes place where an acetate from the iodine structure acts as a base taking the Cβ proton, finally obtaining iodine byproduct (3-oxo-1,3-dihydroisobenzofuran-1-yl acetate), the ketone, and a second molecule of acetic acid (Scheme 4.22).

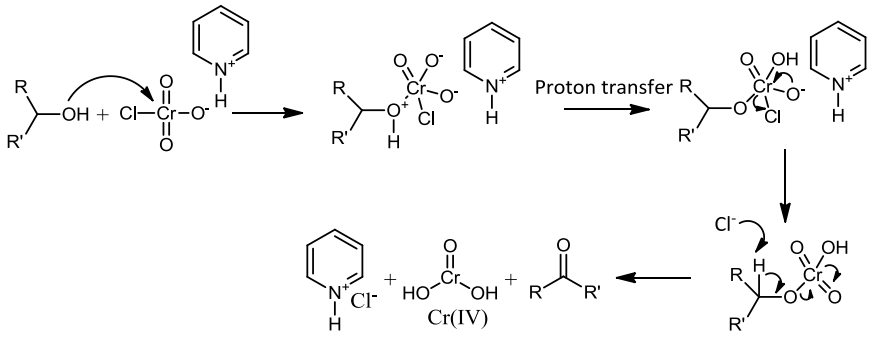


Scheme 4.22. *Proposed mechanism for the Dess-Martin oxidation.*

Nevertheless, despite the fact that we were working at 1.1 eq. of DMP, under very anhydrous conditions or with few equivalents of water (reported to be beneficial in some cases[54], and very short reaction times (30 minutes) in all cases we obtained 60-65% elimination product and 40-35% of the remaining alcohol in the reaction crude.

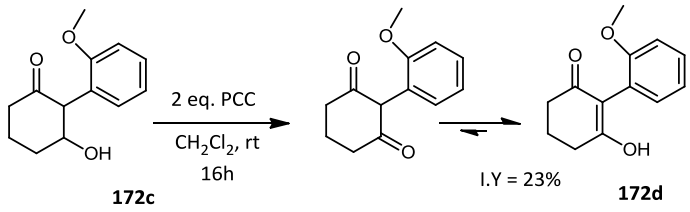
Our last attempt to oxidize C-OH to C=O involved PCC (pyridinium chlorochromate) and PDC (pyridinium dichromate)[28]. Using chromium reagents for industrial purposes is highly unrecommended, due to the toxicity of Cr(VI) species. Nevertheless, we wanted to screen this methodology because mechanistically it doesn't need an external base to promote Cβ-OH deprotonation.

We focused on pyridinium chlorochromate, since it is reported to be used more generally towards secondary alcohol oxidation[28]. Mechanistically, the alcohol coordinates to the Chromium(VI) atom, displacing chlorine, which then acts as a base, resulting in oxidation of the alcohol and reduction of the Chromium (VI) to Chromium (IV) (Scheme 4.23).



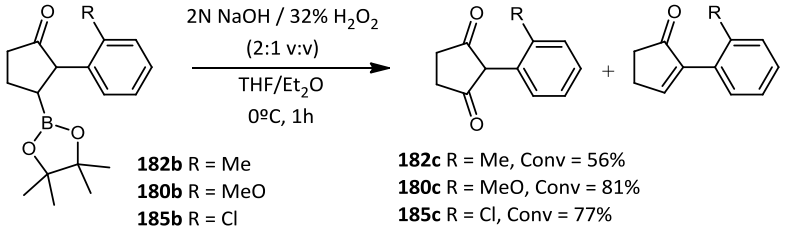
Scheme 4.23. *Proposed mechanism for the PCC oxidation.*

We explored the oxidation of 2-orthomethoxyphenyl 3-hydroxy cyclohexanone **172c** under the reaction conditions based on PCC as oxidative reagent[29] (Scheme 4.24). The desired product was isolated in 23% yield and NMR spectra allowed to characterize it as the corresponding enol. Apparently, such types of diones that perform keto-enol tautomerism are reported to be more stable in the enol form[30]



Scheme 4.24. *Oxidation of 2-orthomethoxyphenyl-3-hydroxycyclohexanone.*

Next, we conducted a similar study on the oxidation of α-aryl-β-boryl cyclopentanones. We carried out an oxidative work up to transform the C-B bond into C=O bond, with the three model β-borated ortho-substituted 2-aryl cyclopentanones **180b**, **182b**, **185b**. The dropwise addition of a solution that contains NaOH (2N) /32% H_2O_2 (2:1 v/v) in THF/Et_2O (1:1 v/v) at 0ºC for 1 hour allowed to extract the corresponding 2-aryl-1,3-cyclopentanediones (Scheme 4.25) in good conversion. It was possible to observe the corresponding 2-aryl-cyclopent-2-enone due to an acid-base pinacolboryl elimination process.



Scheme 4.25. *Oxidation of 2-aryl-3-pinacolboryl cyclopentanones towards 2-aryl-1,3-cyclopentanediones.*

Since we have been able to conduct the synthesis of 2-aryl-1,3-cyclohexanediones and 2-aryl-1,3-cyclopentane diones stepwise, we next planned to conduct the global synthesis from the corresponding α-iodoenone in a one pot protocol. Towards this end, we conducted the transformation of α-iodocyclopentenone into 11 different examples of 2-aryl-1,3-cyclopentanediones, working at 0.5 mmol scale. Significant higher values on the conversion of 2-aryl-1,3-cyclopentanediones **182c**, **180c** and **185c** (Table 4.7 entries 1-3) could be achieved in the one pot synthesis, compared with the stepwise procedure (Scheme 4.25). Interestingly, aryl groups with electron donating substituents seem to favor the completion of the three reactions with high conversions and therefore isolated yields. This is the case of the 2-aryl-1,3-cyclopentanediones **177c**, **181c**, **183c** and **184c** (Table 4.7, entries 4, 11, 7, 8) being 2-(2,4,5-trimethylphenyl)cyclopentane-1,3-dione (**184c**) and 2-(naphthalene-1-yl)cyclopentane-1,3-dione (**181c**) synthesized for the first time in this work. On the contrary, aryl groups with electron withdrawing substituents diminish the conversion on the desired 2-aryl-1,3-cyclopentanediones during the oxidation procedure, since the Hα has more acidic properties and promote the H-Bpin elimination under the reaction conditions to give the corresponding 2-aryl-cyclopent-2-enones. However, thinking on a high scale production, the formation of 2-aryl-cyclopent-2-enone as by product could be used by means of recycling, and once obtained, submit it again to the β-boration/oxidation methodology.

In comparison with previously reported methods to synthesize 2-aryl-1,3-cyclopentanediones[6-8,10], the method reported here contributes to minimize multiple steps synthesis and intermediate purifications. The use of α-iodocyclopentenone **168** as starting material and accessible catalysts based on Pd/C and CuCl encourages the scaling up and the dignification of the global process.

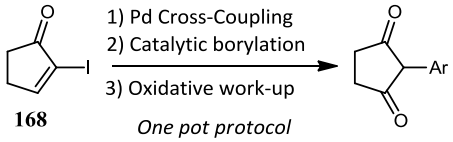
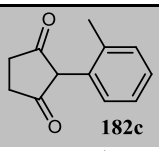
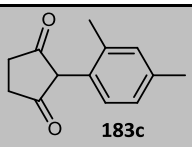
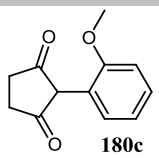
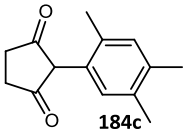
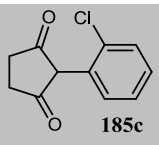
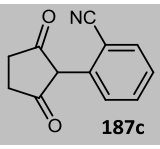
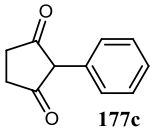
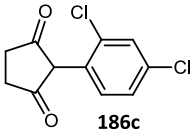
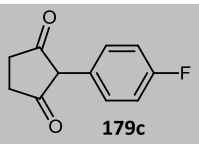
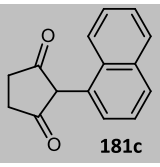
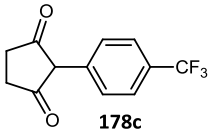


Table 4.8. *One-pot synthesis of 2-aryl-1,3-cyclopentanediones from α-iodocyclopentenone.*

Entry	Product	Conv(%)[c]	I.Y(%)[d]	Entry	Product	Conv(%)[c]	I.Y(%)[d]
1[a]	 **182c**	64	32	**7**[a]	 **183c**	63	28
2[a]	 **180c**	90	34	**8**[a]	 **184c**	48	16
3[a]	 **185c**	85	30	**9**[b]	 **187c**	59	14
4[a]	 **177c**	70	20	**10**[a]	 **186c**	34	20
5[a]	 **179c**	25	17	**11**[a]	 **181c**	63	28
6[b]	 **178c**	30	21				

[a]Standard conditions for 1) cross coupling = **168** (0.5 mmol), Na_2CO_3 (1 mmol), Ar-$B(OH)_2$ **109** (0.55 mmol), 10% Pd/C, DME:H2O (1:1 8 mL), 80ºC, 16h; 2) β-boration = CuCl (3 mol%), PCy_3 (**L20**) (6 mol%), NaOtBu (9 mol%), B_2pin_2 (**1**) (1.1 eq), THF (3 mL), MeOH (2.5 eq.), rt, 16h; 3) Oxidation = 2N NaOH/32% H_2O_2 (2:1 v/V 3.3 mL) in THF/Et_2O (1:1 v/v 3mL:3mL) at 0ºC 1h. [b]Standard conditions: Cross coupling step performed at rt. Oxidation performed at 0ºC within 30 minutes. [c]Conversion determined by ^{1}H NMR and GC analysis. [d]I.Y. = Isolated yield based upon an average of two runs.

We were pleased to conduct the synthesis of 2-aryl-1,3-cyclopentanediones in a one pot reaction protocol, improving the isolated yields from the previous reported methods[33-35,37], and also, being able to synthesize compounds **180c**, **178c**, **184c**, **187c** and **181c** for the first time in this work.

The analogue one pot protocol for the synthesis of 2-aryl-1,3-cyclohexanediones has not been covered due to the limitations we found in the last step, based on the two oxidative pathways.

4.4 Conclusions

1. The study of a new method to synthesize 2-aryl-1,3-diones has been carried out in a stepwise protocol and one pot protocol.

2. The easy preparation of α-iodoenones is the starting point for a convenient synthesis of 2-aryl-1,3-cyclodiones.

3. The cross-coupling between α-iodoenones and arylboronic acids, by means of palladium complexes, allows to obtain 2-aryl-cyclohexenones and 2-aryl-cyclopentenones with high conversion and isolated yield.

4. The key step on the synthesis of 2-aryl-1,3-diones is the copper catalyzed β-borylation of 2-aryl-cyclohexenones and 2-aryl-cyclopentenones. Up to 20 new compounds have been synthesized for the first time in this work.

5. The 2-aryl-3-boryl-cyclohexanones and 2-aryl-3-boryl-cyclopentanones have been prepared as simple *trans* diaestereomers in mostly of the examples,or as a favored *trans*/*cis* diaestereomeric ratio.

6. Oxidation of 2-aryl-3-boryl-cyclopentanones can be efficiently carried out using H_2O_2/NaOH from the C-B to the C=O bond.

7. Oxidation of 2-aryl-3-boryl-cyclohexanones is more dependent of the nature of the oxidation reagent and bases have to be avoided to diminish the Cα-H elimination to form the 2-aryl-cyclohexenones. PCC (pyridinium chlorochromate) seems to be a convenient oxidation reagent.

8. The one pot synthesis of 2-aryl-1,3-cyclopentanediones has been conducted from α-iodocyclopentenone without intermediate purification, with an improved isolated yield compared with previous reported methods. Up to 11 examples have been studied and 5 of them are prepared for the first time in this work.

4.5 References

[1] M. Muehlebach, F. Cederbaum, D. Cornes, A. A. Friedmann, J. Glock, G. Hall, A. F. Indolese, D. P. Kloer, G. L. Goupil, T. Maetzke, H. Meier, R. Schneider, A. Stoller, H. Szczepanski, S. Wendeborn, H. Widmer, *Pest. Manag. Si.,* **2011**, *67*, 1499.

[2]E. C. Oerke, H. W. Dehne , *Crop. Pro.,* **2004***, 23*, 275.

[3] J. Wanger, T. Niderman in *Modern Crop Protection compounds*, Wiley, **2007**, volume 1, 335.

[4] J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360.

[5] M. Storgaard, F. Z. Dörwald, B. Peschke, D. Tanner, *J. Org. Chem*. **2009**, *74*, 5032.

[6] a) A. Bayer, *WO 9504719*, **1995;** b) U. Wachendorff, E. Brück, A. Elbert, R. Fischer, R. Nauen, N. Stumpf, R. Tiemann, *Proceedings of the Brighton Crop Protection Conference— Pests and Diseases*, **2000**, *2*, 53

[7] S. Ke, T. Sun, Z. Zhang, Y. –N. Zhang, Y. Liang, K. Wang, Z. Yang, *Bull. Korean Chem. Soc.* **2010**, *31*, 2315.

[8] X. –G. Guo, L. –Z. Xu, F. –R. Kong, H. –X. Li, R. –F. Yin, *Chem. Res. Chinese Universities*, **2011**, *27*, 968.

[9] a) A. Mallinger, T. Le Gall, C. Mioskowski, *Synlett* **2008**, *386*, 28.; b)A. Mallinger,T. Le Gall, C. J. Mioskowski, *J. Org. Chem.* **2009**, *74*, 1124.

[10] Th. N. Wheeler, **1982**, US 4338122 A.

[11] L. Zhang, J. Cheng, B. Carry, Z. Hou, *J.Am.Chem.Soc*. **2012**, *134*, 14314.

[12] R. Alfaro, A. Parra, J. Alemán, J. L. García-Ruano, M. Tortosa, *J. Am. Chem. Soc*, **2012**, *134*, 15165.

[13] H. Yoshida, I. Kageyuki, K. Takaki *Org. Lett*, **2013**, *15*, 952.

[14] K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J*, **2014**, *20*, 12032.

[15] N. Miyaura, A. Suzuki *Chem. Rev,* **1995**, *95*, 2457.

[16] F. –X. Felpin *J. Org. Chem,* **2005**, *70*, 8575.

[17])F. Nahra, Y. Macé, D. Lambin, O. Riant, *Angew. Chem. Int. Ed*. **2013**, *52*, 3208.

[18] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald *J. Am. Chem. Soc*., **2005**, *127*, 4685.

[19] a) D. G. Hall, Ed. in *Boronic Acids-Preparation, Applications in Organic Synthesis and Medicine*, 2nd Edition, **2011**, Wiley-VCH:Weinheim; b) E. Fernández, A. Whiting, Topics in Organometallic Chemistry, **2015**, Springer.

[20] J. Cid, H. Gulyás J. J. Carbó, E. Fernández, *Chem. Soc. Rev*, **2012**, *41*, 3558.

[21] a) K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett*. **2000**, *982*; b)H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett*., **2000**, *41*, 6821; c) S. Mun, J. E. Lee, J. Yun *Org. Lett.,* **2006**, *8*, 4887

[22] a) A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int Ed.*, **2010**, *49*, 5130; b) C. Pubill-Ulldemolins, A. Bonet, C. Bo, H. Gulyás, E. Fernández, *Chem. Eur. J.* **2012**, *18*, 1121.

[23] a) M. J. O'Donnell, J. T. Cooper, M. M. Marder *J. Am. Chem. Soc.* **2003**, *125*, 2370; b) A. Chen, L. Ren, C. M. Crudden *J. Org. Chem.* **1999**, *64*, 9704; c) R. Larouche-Gauthier, T. G. Elford, V. K. Aggarwal *J. Am. Chem. Soc.* **2011**, *133*, 1647; d) C. M. Crudden, D. Edwards *Eur. J. Org. Chem.* **2003**, 4695; e) E. Fernández, K. Maeda, W. Hooper J. M. Brown, *Chem. Eur. J.* **2000**, *6*,1840.

[24] G. W. Kabalka, T. M. Shoup, N. M. Goudgaon *J. Org. Chem.* **1989**, *54*, 5930.

[25] N. Mori, H. Togo, *Tetrahedron*, **2005**, *61*, 5915.

[26] E. J. Corey, C. U. Kim, *J. Am. Chem. Soc.,* **1972**, *94*, 7586.

[27] a) D. B. Dess, J. C. Martin., *J. Am. Chem. Soc.,* **1991**, *113*, 7277; b) S. D. Meyer, S.L. Schreiber *J. Org. Chem.* **1994**, 59, 7549.

[28] G. Tojo, M. Fernández (**2006**), *Oxidation of alcohols to aldehydes and ketones. A guide to current common practice.* Santiago de compostela, Spain. Springer.

[29] J. Carr, T.S. Snowden, *Tetrahedron.,* **2008**, *64*, 2897.

[30] T. Wheeler, *J. Org. Chem.,* **1979**, *44*, 4906.

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

5. Conclusions

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

***5.1. Chapter 2*. Sequential C-B and C-F bond formation. A new approach towards vicinal difunctionalization.**

In this chapter we have screened and developed methodologies towards the difunctionalization of α,β-unsaturated carbonyl compounds, involving fluorine and boron chemistry. A key aspect towards the synthesis of the mentioned compounds was the enol/enolate stability in the cycle in order to react with a F^+ source once the borylation has taken place.

Concerning the metal-catalyzed approach, we have seen that a desired protocol to obtain the α-fluoro β-boryl ketones consist on using a very specific type of copper precursor ($CuPF_6(CH_3CN)_4$ and base (LiOtBu) in a polar aprotic solvent such as DMF. The induction time for the formation of the 1,4-diborated product was crucial; longer times than 2h led in the end to a mixture of fluorinated-borylated regioisomers.

In all the cases studied, the conversion, chemo- and regioselectivity were moderate to high. It is worth to note that diaestereoselection was substrate dependant, obtaining for the cases studied, the best diaestereselection for the β-methyl substituted cyclohexenone. Also, in this very concrete case of good diaestereoselection, we could induce enantioinduction up to 73% by performing the borylation pathway with (R,R)-QuinoxP ligand.

While screening the metal free context for this transformation, the acid catalyzed fluorination of already formed β-borylated ketones was a key point. We formed an enol catalyzed by the acid that could interact with the electrophilic fluorinating reagent, with complete regioselection towards the α'-fluoro β-boryl compounds. In those cases, diaestereoselection was close to 1/1.

As a limitation, the acid-catalyzed fluorination of β-borylated ketones could only be performed on linear substrates. Eventually, we have been able to apply a new methodology towards the synthesis of α-fluoro and α'-fluoro β-boryl compounds with no precedents in the literature.

5.2. Chapter 3. Construction of vicinal C-B and C-X (X = Cl, Br) bonds.

In this chapter we screened methodologies concerning the difunctionalization of α,β-unsaturated carbonyl compounds involving halogenation and borylation chemistry.

We had the precedent in the literature that fluorination/borylation of α,β-unsaturated carbonyl compounds could be performed using a metal-catalyzed approach, however, the reactivity of the chosen electrophilic halogenating reagents N-chlorosuccinimide and N-bromosuccinimide didn't seem to fully suit our expectations. 4-hexen-3-one was not halogenated, and 2-cyclohexen-1-one could be halogenated in a 88% chemoselection, but a complex mixture of halogenated/borylated regioisomers was obtained.

Therefore this methodology has some limitations, but we were delighted to discover that β-substituted α,β-unsaturated cyclic enones gave better results in terms of chemoselection and regioselection. Optimized conditions and substrate screening concerning different substitution on the β-carbon of the β-substituted cyclic enones, led to a wide array of α-chlorinated β-borylated and α-brominated β-borylated carbonylic compounds with no precedent in the literature, all of them obtained in good to moderate yields.

In comparison, bromination with NBS was less efficient than chlorination with NCS. We attribute this fact to the increasing size of the halogen (Br>Cl) thus having an increasing difficulty to interact with the in-situ formed enolate.

In an attempt to increase the substrate scope, we approached the selective α-chlorination of α,β-unsaturated carbonyl compounds. We successfully synthesized up to 10 different α-halogenated substrates using an existing methodology. Several attempts towards the borylation of those newly synthesized compounds finally led to the desired chemoselection for the α-chloro 2-cyclohexen-1-one and α-chloro 3-methyl-2-cyclohexen-1-one. However, the other substrates used led towards no conversion to any product. We attribute this fact again to steric interactions of the halogen on the α-position, that won't allow the LCu-Bpin nucleophilic species interact with the electrophilic Cβ of the α,β-unsaturated substrate. Nevertheless, still a consistent amount of α-halogenated (chlorinated and brominated) β-borylated carbonyl compounds were obtained, being this a pioneering work in the area consisting on the nucleophilic boron addition and in situ electrophilic halogen addition to α,β-unsaturated carbonyl compounds.

***5.3. Chapter 4*. One-pot synthesis of 2-aryl-1,3-diones through catalytic borylation as a key sequence.**

In this chapter we performed a study for a new method to synthesize 2-aryl-1,3-diones, which has been carried out in a stepwise protocol and one pot protocol.

The easy preparation of α-iodoenones is the starting point for a convenient synthesis of 2-aryl-1,3-cyclodiones. The cross-coupling between α-iodoenones and arylboronic acids, by means of palladium complexes, allows to obtain 2-aryl-cyclohexenones and 2-aryl-cyclopentenones with high conversion and isolated yield. The key step on the synthesis of 2-aryl-1,3-diones is the copper catalyzed β-borylation of 2-aryl-cyclohexenones and 2-aryl-cyclopentenones. Up to 20 new compounds have been synthesized for the first time in this work.

The 2-aryl-3-boryl-cyclohexanones and 2-aryl-3-boryl-cyclopentanones have been prepared as simple *trans* diaestereomers in most of the examples, or as a favored *trans*/*cis* diaestereomeric ratio.

Oxidation of 2-aryl-3-boryl-cyclopentanones can be efficiently carried out using H_2O_2/NaOH from the C-B to the C=O bond. Oxidation of 2-aryl-3-boryl-cyclohexanones is more dependent of the nature of the oxidation reagent. Bases have to be avoided to diminish the Cα-H elimination to form the 2-aryl-cyclohexenones. PCC (pyridinium chlorochromate) seems to be a convenient oxidation reagent.

The one pot synthesis of 2-aryl-1,3-cyclopentanediones has been conducted from α-iodocyclopentenone without intermediate purification, with an improved isolated yield compared with previous reported methods. Up to 11 examples have been studied and 5 of them are prepared for the first time in this work.

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

6. EXPERIMENTAL SECTION

Table of contents:

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

6.1. General considerations

Unless otherwise noted, all manipulations were performed under an argon atmosphere using standard Schlenk-type glassware. Pyridine (Py) was distilled on KOH under an argon atmosphere then degassed. Methanol (MeOH) was destilled on CaH_2. Toluene was distilled on sodium under an argon atmosphere then degassed. Dry Tetrahydrofuran (THF) and dichloromethane (DCM) were used right after distillation from the distillation devices. Dimethylformamide 98% anhydrous (DMF), 1,2-Dimethoxyethane 99.5% anhydrous (DME), 1,2-Dibromoethane 98% anhydrous were used directly from the suppliers Sigma Aldrich. Solvents used for workup were of technical grade. The rest of reagents were provided by Sigma-Aldrich or Alfa Aesar.

-NMR spectra were obtained on either a Varian Gemini 300 or Varian Mercury 400 spectrometer. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane. ^{19}F NMR chemical shifts are reported in ppm (δ) relative to hexafluorobenzene. $^{11}B\{^{1}H\}$ NMR chemical shifts are reported in ppm (δ) relative to $BF_3(CH_3)_2O$.

-G.C. was equipped with column HP-5.

Initial temp 80ºC, initial time 3min.
rate 15ºC/min
Pressure 100 KPa
Temp injector 225 ºC
Temp detector 250 ºC

-G.C-Mass was equipped using a HP-5MS capillary column (30m X 0.25 mm X 0.25 m). MS (70eV); m/z: (M^+).

Initial temp 80ºC, initial time 3min.
rate 15ºC/min
Pressure 100 KPa
Temp injector 225 ºC
Temp detector 250 ºC

-ESI-TOF accurate mass analyses were carried using a 6210 Time of Flight (TOF) mass spectrometer from Agilent Technologies (Waldbronn, Germany) with an ESI interface.

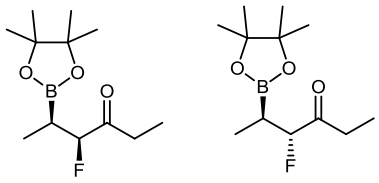
6.2. Chapter 2: Sequential C-B and C-F bond formation. A new approach towards difunctionalization

6.2.1 General procedure for the Cu-catalyzed β-boration-α-fluorination of α,β-unsaturated ketones

$Cu(CH_3CN)_4PF_6$ (0.025mmol), bis(pinacolato)diboron (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (0.025 mmol) were transferred into an oven-dried Schlenck tube under Argon atmosphere. DMF (2 mL) was then added. The mixture was stirred for 10 minutes at room temperature before the α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 2.5 hours. Afterwards, the fluorinating reagent F-TEDA-BF_4 (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. After 16 hours the reaction was quenched with EtOAc (4 mL) and water (2 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40ºC. An aliquot was diluted in deuterated chloroform and analyzed by G.C and ^{1}H NMR to determine conversion and selectivity[1,2].

Selected NMR data:

4-fluoro-5-pinacolboryl-hexan-3-one (purified as an enriched diastereomeric mixture on the *syn*-α-fluoro β-boryl ketone).



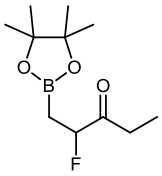
88 **88'**

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 4:1). Despite the fact that the major diastereomer in the reaction crude was the *anti*-α-fluoro β-boryl ketone, the purification provided an enriched mixture on the *syn*-α-fluoro β-boryl ketone. Product **88** was obtained in a 30% I.Y. as a pale yellow solid.

Diastereomer *anti*-**88'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (dd J = 48 Hz, J = 8 Hz, 1H), 2.73 (q, J = 3 Hz, 2H), 1.35 (m, 1H), 0.95 (s, 12H), 0.76 (t, J = 8 Hz, 3H), 0.75 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 99.95, 83.59, 60.36, 32.14, 29.68, 24.75, 24.63, 14.16; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.22. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -192.8 (dd, J = 48 Hz, J = 22 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{12}H_{22}BFO_3$) = Calculated 267.1544 ($M+Na^+$) / Found 267.1539 ($M+Na^+$).

Diastereomer *syn*-**88**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.87 (dd J = 48 Hz, J = 4 Hz, 1H), 2.68 (q, J = 3 Hz, 2H), 1.35 (m, 1H), 0.95 (s, 12H), 0.76 (t, J = 8 Hz, 3H), 0.75 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 99.95, 83.59, 60.36, 32.14, 29.68, 24.75, 24.63, 14.16; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.22. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -191.5 (dd, J = 48 Hz, J = 26 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{12}H_{22}BFO_3$) = Calculated 267.1544 ($M+Na^+$) / Found 267.1539 ($M+Na^+$).

4-fluoro-5-pinacolboryl-pentan-3-one.

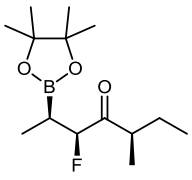


95

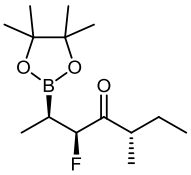
The product **95** could not be isolated as pure product. NMR data are extracted from the crude of reaction mixture.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.93 (dt J = 48 Hz, J = 8 Hz, 1H), 2.50 (q, 2H), 1.2-1.1 (s, 12H), 0.95 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -181.0 (dt, J = 48 Hz, J = 28 Hz, 1F).

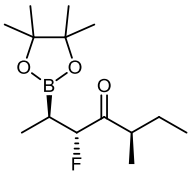
3-fluoro-2-pinacolboryl-5-methyl 4-heptanone.



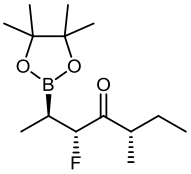
96



96'



96''



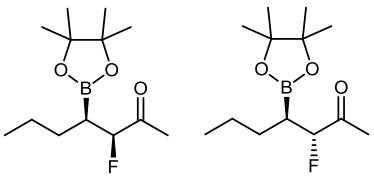
96'''

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 4:1) as a diaestereomeric mixture *syn*/*anti* (22/78). Product **96** was obtained in a 60% I.Y. as a white solid.

96'': ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.88 (dd J = 48 Hz, J = 12 Hz, 1H), 2.50 (m, 1H), 1.2-1.1 (s, 12H), 1.01 (d, J = 8 Hz, 3H), 0.98 (q, J = 8 Hz, 2H). 0.80 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -193.48 (dt, J = 48 Hz, J = 25 Hz, 1F). **96'''**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.85 (dd J = 48 Hz, J = 24 Hz, 1H), 2.50 (m, 1H), 1.2-1.1 (s, 12H), 1.01 (d, J = 8 Hz, 3H), 0.98 (q, J = 8 Hz, 2H). 0.80 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -193.61 (dt, J = 48 Hz, J = 24 Hz, 1F). **96'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.97 (dd J = 48 Hz, J = 6 Hz, 1H), 2.50 (m, 1H), 1.2-1.1 (s, 12H), 1.01 (d, J = 8 Hz, 3H), 0.98 (q, J = 8 Hz, 2H). 0.80 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -191.27 (dd, J = 48 Hz, J = 20 Hz, 1F). **96**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.95 (dd J = 48 Hz, J = 6

Hz, 1H), 2.50 (m, 1H), 1.2-1.1 (s, 12H), 1.01 (d, J = 8 Hz, 3H), 9.98 (q, J = 8 Hz, 2H). 0.80 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -191.71 (dt, J = 48 Hz, J = 20 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{14}H_{26}BFO_3$) = Calculated 295.1857 ($M+Na^+$) / Found 295.1857 ($M+Na^+$).

3-fluoro-4-(pinacol)boryl-2-heptanone.

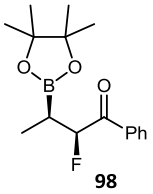


97 **97'**

The product **97** could not be isolated as pure product. NMR data are extracted from the crude of reaction mixture .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.76 (dd J = 52 Hz, J = 12 Hz, 1H), 2.30 (s, 3H), 1.5-1.2 (m, 8H), 1.2-1.1 (s, 12H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -193.48 (dt, J = 50 Hz, J = 15 Hz, 1F). **100'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (dd J = 52 Hz, J = 4 Hz, 1H), 2.31 (s, 3H), 1.5-1.2 (m, 8H), 1.2-1.1 (s, 12H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -186.19 (dt, J = 50 Hz, J = 30 Hz, 1F).

1-phenyl-2-fluoro-3-pinacolboryl butan-1-one.

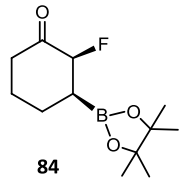


98

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 4:1). Despite the fact that the major diastereomer in the reaction crude was the *anti*-α-fluoro β-boryl ketone, the purification provided only the *syn*-α-fluoro β-boryl ketone. Product **98** was obtained in a 17% I.Y. as a pale yellow solid.

Diastereomer *syn*-**98**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (m, 1H), 7. 39 (m, 2H), 7.25 (m, 2H), 5.67 (dd J = 48 Hz, J = 4 Hz, 1H), 2.45 (m, 1H), 1.2-1.1 (m, 12H), 1.05 (d, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.15, 133.30, 129.32, 128.39, 127.98, 127.30, 125.78, 96.02, 83.64, 32.14, 30.93, 24.83, 24.70, 24.64, 16.28; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.86. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -183.62 (dd, J = 48 Hz, J = 15 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{16}H_{22}BFO_3$) = Calculated 315.1544 ($M+Na^+$) / Found 315.1544 ($M+Na^+$).

2-fluoro-3-pinacolboryl cyclohexan-1-one.

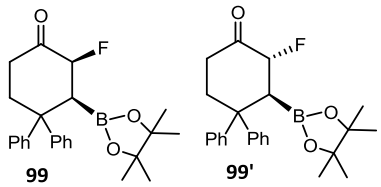


84

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 2:1). Despite the fact that the major diastereomer in the reaction crude was the *anti*-α-fluoro β-boryl ketone, the purification provided only the minor diastereoisomer *syn*-α-fluoro β-boryl ketone. Product **84** was obtained in a 20% I.Y. as a yellow solid

Diastereomer *syn*-**84**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.85 (dd J = 48 Hz, J = 4 Hz, 1H), 2.55 (m, 2H), 2.0-1.5 (m, 6H), 1.2-1.1 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.34, 94.59, 83.74, 42.55, 41.84, 28.41, 26.46, 24.83, 24.70, 24.64, 22.67; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.26. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -187.30 (ddd, J = 48 Hz, J = 30 Hz, J = 7 1F). HRMS ESI-TOF(m/z) ($C_{12}H_{20}BFO_3$) = Calculated 265.1387 ($M+Na^+$) / Found 265.1383($M+Na^+$).

2-fluoro -3-(pinacol)boryl 4,4-diphenyl-cyclohexan-1-one.

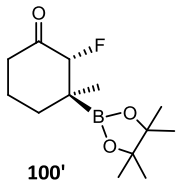


99 **99'**

This product was purified by recrystallisation. As a mixture of both diastereoisomers, being the major the *anti*-α-fluoro β-boryl ketone. Product **99** was obtained in a 90% I.Y. as a white solid.

Diastereomer *anti*-**99'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5-7.0 (m, 10H), 4.31 (dd J = 48 Hz, J = 12 Hz, 1H), 3.5-2.0 (m, 5H), 1.1-0.75 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.34, 145.56, 126.78, 125.33, 125.12, 124.96, 124.77, 123.53, 123.36, 123.12, 92.59, 84.74, 37.65, 31.84, 28.41, 26.46, 24.83, 24.64, 22.67; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.25. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -187.71 (dd, J = 48 Hz, J = 7.5 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{24}H_{28}BFO_3$) = Calculated 417.2013 ($M+Na^+$) / Found 417.2011 ($M+Na^+$) Diastereomer *syn*-**99**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5-7.0 (m, 10H), 4.28 (dd J = 48 Hz, J = 8 Hz, 1H), 2), 3.5-2.0 (m, 5H), 1.1-0.75 (s, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): 203.67, 143.56, 126.78, 125.33, 125.12, 124.96, 124.77, 123.53, 123.36, 123.12, 91.89, 84.70, 37.61, 31.84, 28.35, 26.76, 25.82, 24.53, 22.99; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 33.25. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -185.96 (dd, J = 48 Hz, J = 15 Hz, J = 7 1F). HRMS ESI-TOF(m/z) ($C_{24}H_{28}BFO_3$) = Calculated 417.2013 ($M+Na^+$) / Found 417.2011 ($M+Na^+$)

2-fluoro -3-pinacolboryl 3-methyl-cyclohexan-1-one (purified as the *anti*-α-fluoro β-boryl ketone).



100'

This product was purified by recrystallisation as the *anti*-α-fluoro β-boryl ketone. Product 103 was obtained in a 87% I.Y. as a pale yellow solid.

Diastereomer *anti*-**103'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.93 (dd J = 48 Hz, J = 4 Hz, 1H), 2.5-1.7 (m, 6H), 1.1-0.75 (s, 12H), 1.0 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.34, 145.56, 126 92.59, 84.74, 37.65, 31.84, 28.41, 26.46, 24.83, 24.64, 22.67; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.82. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -195.35 (dt, J = 48 Hz, J = 7 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{13}H_{22}BFO_3$) = Calculated 279.1544 ($M+Na^+$) / Found 279.1543.1936 ($M+Na^+$).

6.2.2 General procedure for the enantioselective Cu-catalyzed β-boration α-fluorination of 3-methyl-2-cyclohexen-1-one

$Cu(CH_3CN)_4PF_6$ (0.025mmol), bis(pinacolato)diboron (0.35 mmol), LiOtBu (0.015 mmol), QuinoxP* (0.025 mmol) were transferred into an oven-dried Schlenck tube under Argon atmosphere. DMF (2 mL) was then added. The mixture was stirred for 10 minutes at room temperature before the 3-methyl 2-cyclohexen-1-one (0.25 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 2 hours. Afterwards, the fluorinating reagent F-TEDA-BF_4 (0.5 mmol) was added to the reaction mixture and the reaction was stirred at room temperature for 16 hours. After 16 hours the reaction was quenched with EtOAc (4 mL) and water (2 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40ºC. An aliquot was diluted in deuterated chloroform and analyzed by G.C. and ^{1}H NMR to determine conversion and diastereoselectivity. The ee values were determined on HPLC column IA, flow: 1ml/min, hexane/IPA (99.8/0.2)[1,2].

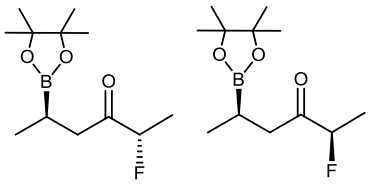
6.2.3 General procedure for the organocatalytic β-boration of α,β-unsaturated carbonyl compounds followed by acid catalyzed α-fluorination

Diboron reagent (1.1 eq. 0.27 mmol), (normally bis(pinacolato)diboron), NaOtBu (5 mol% 0.01 mmol) and PCy_3 (10 mol%, 0.025 mmol) were transferred into an oven-dried Schlenck tube under Argon atmosphere. MeOH (2 mL) was then added. The mixture was stirred for 10

minutes at room temperature before the α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction was stirred at 70ºC for 2 hours (unless longer time is required to complete the β-boration step). After that period, an aliquot was analyzed by GC to determine the complete β-boration-α-protonation of the substrate. Afterwards, catalytic amounts of H_2SO_4 95% (10 mol%, 0.02 mmol), and fluorinating reagent (2 eq., 0.50 mmol) (normally F-TEDA-BF_4) were added and the reaction was led overnight heating at 50ºC. The reaction mixture was cooled down, the precipitate formed was filtered and the solvent removed by rotary evaporation. Afterwards, EtOAc (4 ml) and water (2 ml) were added to the dry crude reaction mixture. The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40ºC. An aliquot was diluted in deuterated chloroform and analyzed by G.C and ^{1}H NMR to determine conversion[2,3].

Selected NMR data:

2-fluoro-5-pinacolboryl-hexan-3-one.

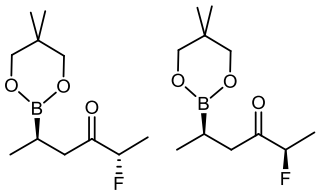


87 **87'**

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 4:1). Product **87** was obtained in a 71% I.Y. as a yellow oil. Diastereoselection *anti/syn* =1/1.

Diastereomer **87**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (dq J = 48 Hz, J = 8 Hz, 1H), 2.71 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 2.67 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 1.40 (dd J = 20 Hz, J = 8 Hz, 3H), 1.22 (m, 1H) 1.17 (s, 6H), 1.15 (s, 3H), 1.14 (s, 3H), 0.93 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 92.48 (J = 180Hz), 83.07, 46.20, 41.43, 24.62, 17.65, 14.98; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.03. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.6 (dqt, J = 48 Hz, J = 20 Hz, J = 3 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{12}H_{22}BFO_3$) = Calculated 267.1544 ($M+Na^+$) / Found 267.1542 ($M+Na^+$) .Diastereomer **87'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.80 (dq J = 48 Hz, J = 8 Hz, 1H), 2.60 (ddd, J = 16 Hz, J = 6 Hz, J = 3 Hz, 1H), 2.56 (ddd, J = 16 Hz, J = 6 Hz, J = 3 Hz, 1H), 1.39 (dd J = 20 Hz, J = 8 Hz, 3H), 1.19 (m, 1H), 1.17 (s, 6H), 1.16 (s, 3H), 1.15 (s, 3H) 0.92 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 92.47 (J = 180Hz), 83.07, 46.20, 41.43, 24.62, 17.65, 14.98; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 34.03. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.7 (dqt, J = 48 Hz, J = 20 Hz, J = 3 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{12}H_{22}BFO_3$) = Calculated 267.1544 ($M+Na^+$) / Found 267.1542 ($M+Na^+$)

2-fluoro-5-(neopentylglycol)boryl-3-hexanone.

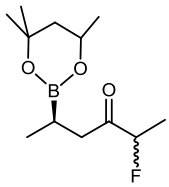


101 **101'**

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 15:1). Product **101** was obtained in a 61% I.Y. as a pale yellow solid. Diastereoselection *anti/syn* =1/1.

Diastereomer **101**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (dq J = 50 Hz, J = 8 Hz, 1H), 3.52 (s, 4H), 2.68 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 2.63 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 1.38 (dd J = 24 Hz, J = 8 Hz, 3H), 1.23 (m, 1H), 0.88 (s, 6H), 0.77 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 92.58 (J = 180Hz), 72.17, 41.62, 31.90, 22.83, 22.05, 17.97, 17.75, 15.63; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.50. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.3 (dqt, J = 50 Hz, J = 24 Hz, J = 3 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{11}H_{20}BFO_3$) = Calculated 253.1387 ($M+Na^+$) / Found 253.1387 ($M+Na^+$) Diastereomer **101'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (dq J = 50 Hz, J = 8 Hz, 1H), 3.52 (s, 4H), 2.55 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 2.49 (ddd, J = 16 Hz, J = 8 Hz, J = 3 Hz, 1H), 1.38 (dd J = 24 Hz, J = 8 Hz, 3H), 1.23 (m, 1H) 0.88 (s, 6H), 0.77 (d, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 92.57 (J = 180Hz), 72.17, 41.53, 31.90, 22.83, 22.05, 17.91, 17.69, 15.68; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.50. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.4 (dqt, J = 50 Hz, J = 24 Hz, J = 3 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{11}H_{20}BFO_3$) = Calculated 253.1387 ($M+Na^+$) / Found 253.1387 ($M+Na^+$)

2-fluoro-5-(hexyleneglycol)boryl-3-hexanone

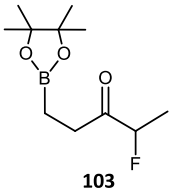


102

The product **102** could not be completely purified by column chromatography from the 5-(hexyleneglycol)boryl-3-hexanone. NMR data are extracted from the mixture. Diastereoselection *anti/syn* =1/1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (dq J = 48 Hz, J = 8 Hz, 1H), 4.2 (m, 1H), 2.60 (m, 1H), 2.55 (m, 1H), 1.63 (dd J = 24 Hz, J = 8 Hz, 3H), 1.24-1.22 (m, 2H), 0.97 (s, 6H), 0.95 (s, 3H), 0.85 (d, overlapped, 3H). ^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.42. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.3 (dqt, J = 50 Hz, J = 24 Hz, J = 3 Hz, 1F).

2-fluoro-5-(pinacol)boryl-3-pentanone

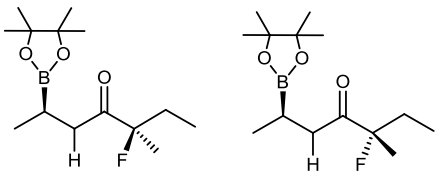


103

The product **103** could not be isolated as pure product. NMR data are extracted from the crude of reaction mixture

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.86 (dq J = 52 Hz, J = 8 Hz, 1H), 2.50-2.40 (m, 2H), 1.50 (dd J = 24 Hz, J = 8 Hz, 3H), 1.2-1.1 (s, 12H), 1.00 (t, J = 8 Hz, 3H). ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -184.9 (dqt, J = 52 Hz, J = 24 Hz, J = 3 Hz, 1F).

3-fluoro, 3-methyl-6-(pinacol)boryl-4-heptanone



104 **104'**

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc, 8:1). Product **104** was obtained in a 51% I.Y as a white crystalline solid. Diastereoselection *anti/syn* =1/1.

Diastereomer **104**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.78 (ddd, J = 20 Hz, J = 8 Hz, J = 4 Hz, 1H), 2.64 (ddd, J = 20 Hz, J = 8 Hz, J = 4 Hz, 1H), 1.90-1.60 (m, 2H), 1.32 (d, J = 20 Hz, 3H), 1.22 (m, 1H) 1.16 (s, 6H), 1.15 (s, 6H), 0.92 (d, J = 8 Hz, 3H), 0.84 (t, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 83.20, 42.45, 31.18, 29.96, 24.96, 22.76, 15.12, 7.6; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 36.2. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -160.4 (tqt, J = 20 Hz, J = 20 Hz, J = 4 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{14}H_{26}BFO_3$) = Calculated 295.1857 ($M+Na^+$) / Found 295.1857 ($M+Na^+$) Diastereomer **104'**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.77 (ddd, J = 20 Hz, J = 8 Hz, J = 4 Hz, 1H), 2.63 (ddd, J = 20 Hz, J = 8 Hz, J = 4 Hz, 1H), 1.90-1.60 (m, 2H), 1.31 (d J = 20 Hz, 3H), 1.22 (m, 1H) 1.16 (s, 6H), 1.15 (s, 6H), 0.91 (d, J = 8 Hz, 3H), 0.82 (t, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 83.20, 42.45, 31.18, 29.96, 24.96, 22.76, 15.12, 7.6; ^{11}B NMR ($CDCl_3$, 128 MHz): δ 36.2. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ -160.7 (tqt, J = 20 Hz, J = 20 Hz, J = 4 Hz, 1F). HRMS ESI-TOF(m/z) ($C_{14}H_{26}BFO_3$) = Calculated 295.1857 ($M+Na^+$) / Found 295.1856 ($M+Na^+$).

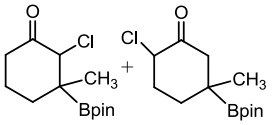
6.3. Chapter 3: Construction of vicinal C-B and C-X (X = Cl, Br) bonds

6.3.1 General procedure for the Cu-catalyzed β-borationa-α-halogenation of α,β-unsaturated ketones

$Cu(CH_3CN)_4PF_6$ (0.025mmol), bis(pinacolato)diboron (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (0.025 mmol) were transferred into an oven-dried Schlenck tube under Argon atmosphere. DMF (2 mL) was then added. The mixture was stirred for 10 minutes at room temperature before the α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 2.5 hours. Afterwards, the electrophilic halogenating reagent (0.5 mmol) was added to the reaction mixture and the reaction was led at room temperature for 16 hours. After 16 hours the reaction was quenched with EtOAc (4 mL) and water (2 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40ºC. An aliquot was diluted in deuterated chloroform and analyzed by G.C and ^{1}H NMR to determine conversion and selectivity[4].

Selected NMR data:

2-chloro-3-pinacolboryl-3-methylcyclohexanone.

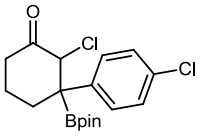


141 **142** (*syn* and *anti*)

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). The products were obtained in 79% I.Y. as a colorless solid. Diastereoselection *anti/syn* =8/1.

141 = ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 4.04 (s, 1H), 2.3 (m, 2H), 2.18 (m,2H), 1.8 (m,2H), 1.21 (s, 12H), 1.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 83.71, 61.92, 46.85, 33.98, 30.60, 24.58, 22.67. ^{11}B NMR ($CDCl_3$, 128 MHz) = 34.22. HRMS ESI-TOF(m/z) ($C_{13}H_{22}BClO_3$) = Calculated 273.1429 ($M+H^+$) / Found 273.1425 ($M+H^+$) **142 (*syn* and *anti*) =** ^{1}HNMR ($CDCl_3$, 400MHz): δ = 4.34 (ddd J= 20 Hz, 12 Hz, 1.21 Hz, 1H), 4.30 (ddd J=12 Hz, 8 Hz, 1.21 Hz, 1H), 2.83 (dd J=12 Hz, 1.21 Hz, 2H), 2.81 (dt J=12 Hz, 1.21 Hz, 2H), 2.5 (d J=8Hz, 2H), 2 (m, 2H), 1.23 (s, 12H), 1.20 (s, 12H), 1.05 (s, 3H), 1.04 (s, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 83.94, 63.31, 49.19, 35.63, 31.25, 24.43, 21.90. ^{11}B NMR ($CDCl_3$, 128 MHz) = 34.22. HRMS ESI-TOF(m/z) ($C_{13}H_{22}BClO_3$) = Calculated 273.1429 ($M+H^+$) / Found 273.1425 ($M+H^+$)

2-chloro-3-pinacolboryl-3-*p*-chlorophenylcyclohexanone.

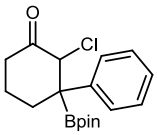


144

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **144** was obtained in 73% I.Y. as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20 (d, 2H), 7.10 (d, 2H), 4.76 (s, J= 2Hz, 1H), 2.90 (td, J = 12Hz, 12Hz, 8Hz, 1H), 2.54 (dt, J = 12Hz, 4Hz, 1H), 2.11 (m, 2H), 1.76 (m, 1H), 1.18 (m, 1H), 1.12 (s, 6H), 1.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 129.10, 128.47, 126.29, 84.57, 64.28, 36.24, 29.90, 27.33, 24.79, 22.02. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 32.72. HRMS ESI-TOF(m/z) ($C_{18}H_{23}BCl_2O_3$) = Calculated 391.1015 ($M+Na^+$) / Found 391.1015 ($M+Na^+$).

2-chloro-3-pinacolboryl-3-phenylcyclohexanone.

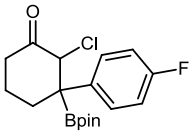


143

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). The product **143** was obtained in 30% I.Y. as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28 (m, 3H), 7.19 (m, 2H), 5.04 (t, 2Hz, 1H), 3.14 (dt, J = 16Hz, 15Hz, 8Hz, 1H), 2.66 (dt, J = 16Hz, 4Hz, 1H), 2.22 (m, 2H), 1.77 (m, 1H), 1.44 (m, 1H), 1.20 (s, 6H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 128.76, 126.68, 126.09, 84.2, 64.28, 36.15, 27.19, 24.31, 21.67. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 33.93. HRMS ESI-TOF(m/z) ($C_{18}H_{24}BClO_3$) = Calculated 357.1405 ($M+Na^+$) / Found 357.1401 ($M+Na^+$).

2-chloro-3-pinacolboryl-3-*p*-fluorophenylcyclohexanone.



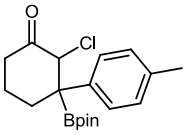
147

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **147** was obtained in 62% I.Y. as a colorless solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.12 (m, 2H), 6.92 (m, 2H), 4.77 (s, 1H), 2.89 (td, J = 12 Hz, 4 Hz, 1H), 2.54 (dt, J = 16Hz, 1H), 2.10 (m, 2H), 1.74 (m, 1H), 1.43 (m, 1H), 1.12 (s, 6H), 1.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 204.80, 128.40, 115.73, 84.29, 64.28, 36.05, 27.20, 24.55, 24.33, 21.77. ^{19} F NMR ($CDCl_3$, 376 MHz): δ = - 116.65 (m). ^{11}B NMR ($CDCl_3$, 128 MHz): δ =

33.48 ppm. HRMS ESI-TOF(m/z) ($C_{18}H_{23}BClFO_3$) = Calculated 375.1311 ($M+Na^+$) / Found 375.1306 ($M+Na^+$).

2-chloro-3-pinacolboryl-3-*p*-methylphenylcyclohexanone

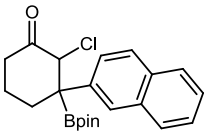


146

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 4:1). Product **146** was obtained in 37% I.Y. as a yellow solid.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (m, 2H), 7.09 (m, 2H), 4.87 (t, 2Hz, 1H), 2.95 (td, J = 12Hz, 12Hz, 8Hz, 1H), 2.58 (td, J = 12Hz, 2Hz, 1H), 2.29 (s, 3H), 2.17 (m, 2H), 1.78 (m, 1H), 1.48 (m, 1H), 1.19 (s, 6H), 1.16 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 204.77, 136.82, 135.47, 129.46, 126.79, 84.12, 64.22, 36.07, 27.13, 24.61, 24.21, 21.71, 20.88. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 35.03. HRMS ESI-TOF(m/z) ($C_{19}H_{26}BClO_3$) = Calculated 371.1561 ($M+Na^+$) / Found 371.1561 ($M+Na^+$).

2-chloro-3-pinacolboryl-3-napthylcyclohexanone.

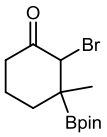


145

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 4:1). Product **145** was obtained in a 50% I.Y. as a white solid.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (m, 2H), 7.63 (m, 1H), 7.49 (m, 2H), 7.30 (m, 2H), 5.04 (s, 1H), 2.98 (td, J = 12Hz, 4Hz, 12Hz, 1H), 2.68 (td, J = 12Hz, J = 12Hz, 2Hz, 1H), 2.33 (m, 1H), 2.19 (m, 1H), 1.80 (m, 1H), 1.46 (m, 1H), 1.20 ppm (s, 6H), 1.15 ppm (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 204.98 ppm, 137.90, 133.43, 131.63, 128.40, 128.06, 127.31, 126.22, 125.87, 125.79, 124.94, 84.32, 64.16, 36.07, 26.98, 24.68, 24.21, 21.72. ^{11}B NMR ($CDCl_3$, 128 MHz): δ = 33.94 ppm. HRMS ESI-TOF(m/z) ($C_{22}H_{26}BClO_3$) = Calculated 407.1561 ($M+Na^+$) / Found 407.1560 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-methylcyclohexanone.

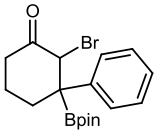


153

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **153** was obtained in a 13% I.Y as a white solid.

^{1}HNMR ($CDCl_3$, 400 MHz): δ = 4.16 (t, J=2Hz, 1H), 3.03 (m, 2H), 2.25 (m, 2H), 1.95 (m, 2H), 1.25 (s, 6H), 1.22 (s, 3H), 1.20 (s,3H), 1.15 (s, 3H) ^{13}CNMR ($CDCl_3$, 100 MHz): δ = 83.98, 60.94, 36.84, 29.13, 24.67, 22.06, 21.20. ^{11}BNMR ($CDCl_3$, 128 MHz): δ = 34.09. HRMS ESI-TOF(m/z) ($C_{13}H_{22}BBrO_3$) = Calculated 339.0743 ($M+Na^+$) / Found 339.0740 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-phenylcyclohexanone.

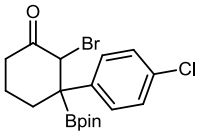


148

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **148** was obtained in a 10% I.Y as a colorless solid.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.29 ppm (m, 3H), 7.19 ppm (m, 2H), 5.04 ppm (s, 1H), 3.13 (td, J = 8Hz, 1H), 2.67 ppm (dt, J = 16Hz, 4Hz, 1H), 2.22 ppm (dd, J = 12Hz, 2H), 1.76 ppm (m, 1H), 1.45 ppm (m, 1H), 1.20 ppm (s, 6H), 1.15 ppm (s, 6H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 205.11 ppm, 140.77, 129.02, 127.03, 126.29, 84.47, 56.37, 35.69, 27.61, 24.83, 21.63. ^{11}B NMR (CD_3Cl, 128 MHz): δ = 32.19 ppm. HRMS ESI-TOF(m/z) ($C_{18}H_{24}BBrO_3$) = Calculated 401.0900 ($M+Na^+$) / Found 401.0904 ($M+Na^+$).

2-bromo-3-pinacolboryl 3- (4-chlorophenyl)cyclohexanone.



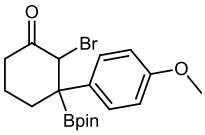
149

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **149** was obtained in a 17% I.Y as a colorless solid.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.27 ppm (d, 8Hz, 2H), 7.15 ppm (d, 2H), 4.97 ppm (s, 1H), 3.15 (td, J = 16Hz, 8Hz, 1H), 2.68 ppm (td, J = 16Hz,4 Hz, 1H), 2.20 ppm (m, 2H), 1.79 ppm (m, 2H), 1.25 ppm (s, 6H), 1.20 ppm (s, 3H), 1.16 ppm (s, 3H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 129.19, 128.55, 126.29, 84.66, 64.52, 36.77, 29.94, 27.55, 24.87, 21.99. ^{11}B NMR (CD_3Cl, 128 MHz): δ =

33.12 ppm. HRMS ESI-TOF(m/z) ($C_{18}H_{23}BBrClO_3$) = Calculated 435.0510 ($M+Na^+$) / Found 435.0510 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-(4-methoxyphenyl)cyclohexanone.

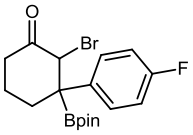


154

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **154** was obtained in a 47% I.Y as a colorless solid.

^1H NMR (CD_3Cl, 400 MHz): δ = 7.05 ppm (d, J = 8Hz, 2H), 6.76 ppm (d, J = 8Hz, 2H), 4.93 ppm (s, 1H), 3.70 ppm (s, 3H), 3.07 (td, J = 16Hz, 8Hz, 1H), 2.57 ppm (td, J = 16Hz ,4 Hz, 1H), 2.14 ppm (m, 2H), 1.70 ppm (m, 2H), 1.12 ppm (s, 6H), 1.08 ppm (s, 6H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 206 ppm, 157.06, 132.15, 127.88, 114.14, 83.15, 56.31, 55.14, 35.45, 27.13, 24.62, 21.35. ^{11}B NMR (CD_3Cl, 128 MHz): δ = 33.12 ppm. HRMS ESI-TOF(m/z) ($C_{19}H_{26}BBrO_4$) = Calculated 431.1005 ($M+Na^+$) / Found 431.1005 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-(4-fluorophenyl)cyclohexanone.

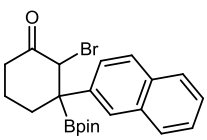


152

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 1:1). Product **152** was obtained in a 17% I.Y as a colorless solid.

^1H NMR (CD_3Cl, 400 MHz): δ = 7.17 ppm (m, 2H), 6.97 ppm (m, 2H), 4.82 ppm (s, 1H), 2.96 ppm (td, J = 12 Hz, 4 Hz, 1H), 2.58 (t, J = 16Hz, 2H), 2.15 ppm (d, J = 12Hz, 2H), 1.79 ppm (m, 1H), 1.15 ppm (s, 6H), 1.09 ppm (s, 6H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 206.05 ppm, 128.73, 115.98, 84.50, 64.53, 36.30, 27.20, 27.45, 24.80, 24.47, 22.02. ^{19}F NMR (CD_3Cl, 376 MHz): δ = -116.65 ppm (m). ^{11}B NMR (CD_3Cl, 128 MHz): δ = 33.35 ppm. HRMS ESI-TOF(m/z) ($C_{18}H_{23}BBrFO_3$) = Calculated 419.0805 ($M+Na^+$) / Found 419.0804 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-(naphthyl)cyclohexanone.

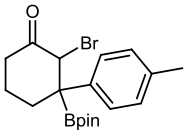


150

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 4:1). Product **150** was obtained in a 27% I.Y as a yellow solid.

^{1}H NMR (CD_3Cl, 400 MHz): δ = δ = 7.60 ppm (m, 7H), 5.18 ppm (s, 1H), 3.16 ppm (td, J = 16Hz, 8Hz, 1H), 2.73 ppm (td, J = 12Hz, 1Hz, 1H), 2.38 ppm (d, J = 16Hz, 1H), 2.20 ppm (d, J = 16Hz, 1H), 1.78 ppm (m, 1H), 1.43 ppm (m, 2H), 1.21 ppm (s, 6H), 1.15 ppm (s, 6H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 204.78 ppm, 138.17, 133.53, 131.50, 128.44, 128.08, 127.30, 126.25, 125.90, 125.84, 124.92, 84.33, 56.02, 35.50, 27.09, 24.72, 24.29, 21.40. ^{11}B NMR (CD_3Cl, 128 MHz): δ = 32.0 ppm. HRMS ESI-TOF(m/z) ($C_{22}H_{26}BBrO_3$) = Calculated 451.1056 ($M+Na^+$) / Found 451.1055 ($M+Na^+$).

2-bromo-3-pinacolboryl-3-(4methylphenyl)cyclohexanone



151

This product was purified by column chromatography (deactivated silica, petroleum ether: EtOAc 4:1). Product **151** was obtained in a 20% I.Y as a white solid.

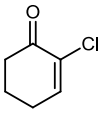
^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.08 ppm (s, 4H), 5.01 ppm (s, 1H), 3.12 ppm (td, J = 16Hz, 8Hz, 1H), 2.64 ppm (td, J = 16Hz, 1Hz, 1H), 2.29 ppm (s, 3H), 2.20 ppm (m, 2H), 1.76 ppm (m, 1H), 1.46 ppm (m, 1H), 1.20 ppm (s, 6H), 1.15 ppm (s, 6H). ^{13}C NMR (CD_3Cl, 100 MHz): δ = 204.95 ppm, 137.32, 135.58, 129.48, 126.66, 84.16, 56.36, 35.47, 27.31, 24.64, 24.29, 21.36, 20.87. ^{11}B NMR (CD_3Cl, 128 MHz): δ = 35.79 ppm. HRMS ESI-TOF(m/z) ($C_{19}H_{26}BBrO_3$) = Calculated 415.1056 ($M+Na^+$) / Found 415.1053 ($M+Na^+$).

6.3.2 General procedure for the synthesis of α-chloroenones

A magnetically stirred solution of α,β-unsaturated ketone (0.518 mmol) in CH_2Cl_2 (4mL) was treated with BAIB bisacetoxyiodobenzene (BAIB) (0.60 mmol) and pyridinium chlorochromate (PCC) or Pyridine.HCl (Py.HCl) (1.25 mmol). The solution was stirred for 16h at which point the starting enone had been consumed. The reaction mixture was diluted with CH_2Cl_2 (5 mL) then washed with HCl (10 mL of a 1M solution). The aqueous phase was extracted with CH_2Cl_2 (2 x 5mL) and the combined prganic extracts washed with brine (5mL) dried ($MgSO_4$), filtered and concentrated in vacuo to afford a yellow oil that was subjected to flash column chromatography and upon collection and evaporation, of the appropriate fractions, the product was characterized by NMR, matching those reported in the literature[4,5].

Selected NMR data:

2-chloro-cyclohex-2-enone.

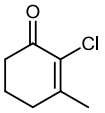


155

This product was purified by flash chromatography silica gel (2:1 (Petroleum ether: Ethyl acetate). Product **155** was obtained in a 67% I.Y. as a yellow solid. Substrate was already reported in *Tetrahedron Letters*, **2009**, *50*, 6008.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.14 ppm (t, J = 4Hz, 1H), 2.57 (m, 2H), 2.48 (m, 2H), 2.09 (m, 2H), ^{13}C NMR (CD_3Cl, 100 MHz): δ = 191.40 ppm, 146.52, 132.17, 38.47, 27.02, 20.99.

2-chloro-3-methylcyclohex-2-enone.

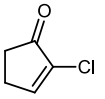


156

This product was purified by flash chromatpgraphy silica gel (2:1 (Petroleum ether: Ethyl acetate). Product **156** was obtained in a 54% I.Y. as a pale yellow solid. Substrate was already reported in *Tetrahedron Letters*, **2009**, 50, 6008.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 2.48 (m, 2H), 2.13 (s, 3H), 1.87 (m, 2H), 1.51 (m, 2H) ^{13}C NMR (CD_3Cl, 100 MHz): δ = 191.37 ppm, 146.52, 130.24, 38.21, 27.13, 24.37, 21.17.

2-chlorocyclopente-2-one.

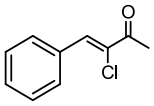


157

This product was purified by flash chromatography silica gel (4:1 (Petroleum ether: Ethyl acetate). Product **157** was purified in a 45% I.Y. as a dark yellow oil. Substrate was already reported in *Tetrahedron Letters*, **2009**, 50, 6008.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.61 (t, J = 4Hz, 1H), 2.68 (m, 2H), 2.51 (m, 2H), ^{13}C NMR (CD_3Cl, 100MHz): δ = 204.1, 169.3, 101.8, 31.1, 30.9.

3-chloro-4-phenyl-but-3-en-2-one.

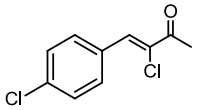


158

This product was purified by flash chromatography silica gel (16:1 (Petroleum ether: Ethyl acetate). Product **158** was purified in a 30% I.Y. as a pale yellow oil. Substrate was already reported in *Tetrahedron Letters*, **2006**, 47, 2863.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.91 ppm (m, 2H), 7.74 (s, 1H), 7.24 (m, 3H), 2.57 (s, 3H) ^{13}C NMR (CD_3Cl, 100 MHz): δ = 193.8, 136.0, 133.3, 131.3, 130.8, 130.6, 129.0, 27.2.

3-chloro-4-(4-chlorophenyl)-but-3-en-2-one.

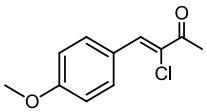


159

This product was purified by flash chromatography silica gel (16:1 (Petroleum ether: Ethyl acetate). Product **159** was purified in a 32% I.Y. as a yellow solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.79 ppm (d, J = 8Hz, 2H), 7.69 (s, 1H), 7.39 (d, J = 8Hz, 2H), 2.53 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.25 ppm, 134.47, 132.01, 128.95, 31.02. HRMS ESI-TOF(m/z) ($C_{10}H_8Cl_2O$) = Calculated 215.0030 ($M+H^+$) / Found 215.0027 ($M+H^+$).

3-chloro-4-(4-methoxyphenyl)-but-3-en-2-one.

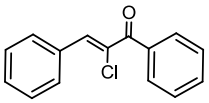


160

This product was purified by flash chromatography silica gel (16:1 (Petroleum ether: Ethyl acetate). Product **160** was purified in a 50% I.Y. as a white solid. Substrate was already reported in *Adv. Synth. Catal.* **2011**, *353*, 871.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.78 (d, J = 4Hz, 2H), 7.61 (s, 1H), 6.80 (d, J = 4Hz, 2H), 3.75 (s, 3H), 2.47 (s, 3H), ^{13}C NMR (CD_3Cl, 100 MHz): δ = 192.6, 136.4, 133.3, 131.7, 131.4, 130.2, 110.7, 129.0, 27.2.

2-chloro-1,3-diphenylprop-2-en-1-one (2-chloro-chalcone).

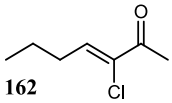


161

This product was purified by flash chromatography silica gel (20:1 (Petroleum ether: Ethyl acetate). Product **161** was purified in a 43% I.Y. as a pale white solid. Substrate was already reported in *Tetrahedron*, **2002**, 58, 7775.

^{1}H NMR (CD_3Cl, 400 MHz): δ = 7.86-7.17 ppm (m, 11H), ^{13}C NMR (CD_3Cl, 100 MHz): δ = 191.1, 139.7, 136.6, 132.4, 130.5, 130.3, 130.2, 129.3, 128.4, 128.3.

3-chlorohept-3-en-2-one.

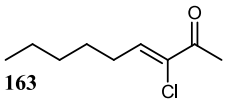


162

This product was purified by flash chromatography silica gel (10:1 (Petroleum ether: Ethyl acetate). Product **162** was purified in a 50% I.Y. as a yellowish oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 6.95 ppm (t, J = 4Hz, 1H), 2.41 (s, 3H), 2.36 (q, J = 8Hz, 2H), 1.54 (q, J = 4Hz, 2H), 0.97 (t, J = 8Hz, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 192.16 ppm, 141.77, 133.82, 31.63, 26.49, 21.13, 13.89. HRMS ESI-TOF(m/z) ($C_7H_{11}ClO$) = Calculated 147.0577 ($M+H^+$) / Found 147.0574 ($M+H^+$).

3-chlorononon-3-en-2-one.

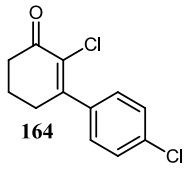


163

This product was purified by flash chromatography silica gel (10:1 (Petroleum ether: Ethyl acetate). Product **163** was purified in a 44% I.Y. as a yellow oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 6.94 ppm (t, J = 8Hz, 1H), 2.40 (s, 3H), 2.37 (q, J = 8Hz, 2H), 1.33 (m, 6H), 0.89 (m, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 192.15 p pm, 142.09, 133.67, 31.49, 29.66, 27.41, 26.48, 22.38, 13.94. HRMS ESI-TOF(m/z) ($C_9H_{15}ClO$) = Calculated 175.0890 ($M+H^+$) / Found 175.0890 ($M+H^+$).

3-(*p*-chlorophenyl)-cyclohexen-2-one.



164

This product was purified by flash chromatography silica gel (10:1 (Petroleum ether: Ethyl acetate). Product **164** was obtained in a 40% I.Y. as a yellow solid.

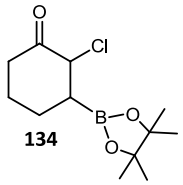
^{1}H NMR (CD_3Cl, 400MHz): δ = 7.40 ppm (d, J = 8Hz, 2H), 7.33 (d, J = 8Hz, 2H), 2.79 (t, J = 4Hz, 2H), 2.70 (t, J = 4Hz, 2H), 2.17 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 191.35 ppm, 155.27, 136.81, 134.76, 128.46, 37.77, 33.97, 22.14. HRMS ESI-TOF(m/z) ($C_{12}H_{10}Cl_2O$) = Calculated 263.0006 ($M+Na^+$) / Found 263.0006 ($M+Na^+$)

6.3.3 General procedure for the Cu-catalyzed β-boration of α-chloroenones

$Cu(CH_3CN)_4PF_6$ (0.025mmol), bis(pinacolato)diboron (0.35 mmol), LiOtBu (0.015 mmol), PCy_3 (0.025 mmol) were transferred into an oven-dried Schlenck tube under Argon atmosphere. DMF (2 mL) was then added. The mixture was stirred for 10 minutes at room temperature before the α-chloro- α,β-unsaturated ketone used as substrate (0.25 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 16 hours. The reaction was quenched with EtOAc (4 mL) and water (2 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated gently on a rotary evaporator at 40ºC. An aliquot was diluted in deuterated chloroform and analyzed by G.C and ^{1}H NMR to determine conversion and selectivity[1].

Selected NMR data:

2-chloro-3-pinacolboryl cyclohexanone.

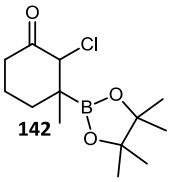


134

This product was purified by column chromatography (deactivated silica, petroleum ether: ethyl acetate 4:1). Product **134** was obtained in a 65% I.Y. as a brownish solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 4.4 ppm (s, 1H), 2.96 (m, 1H), 2.26 (m, 2H), 2.07 (m, 2H), 1,83 (m, 2H), 1.26 (s, 6H), 1.25 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 84.04 ppm, 63.21, 36.75, 27.93, 24.87, 24.59, 21.13. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.3 ppm. HRMS ESI-TOF(m/z) ($C_{12}H_{20}BClO_3$) = Calculated 281.1092 ($M+Na^+$) / Found 281.1090 ($M+Na^+$)

2-chloro-3-pinacolboryl-3-methyl-cyclohexanone.



142

This product was purified by column chromatography (deactivated silica, petroleum ether: ethyl acetate 10:1). Product **142** was obtained in a 45% I.Y as a yellow oil.

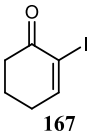
^{1}H NMR (CD_3Cl, 400MHz): δ = 4.04 ppm (s, 1H), 2.82 (m, 1H), 2.20 (m, 2H), 1.93 (m, 2H), 1,56 (m, 1H), 1.23 (s, 12H), 1.18 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 203.39 ppm, 83.93 ppm, 70.44, 38.32, 31.31, 24.50, 24.58, 22.71, 21.83. ^{11}B NMR (CD_3Cl, 128MHz): δ = 37.09 ppm. HRMS ESI-TOF(m/z) ($C_{13}H_{22}BClO_3$) = Calculated 273.1429 ($M+H^+$) / Found 273.1425 ($M+H^+$)

6.4. Chapter 4: One-pot synthesis of 2-aryl-1,3-diones through catalytic borylation as a key sequence

6.4.1 General procedure for the α-iodination of α,β-unsaturated cyclic enones

In a 250 mL round-bottomed three necked flask immersed in a water bath was equipped with an addition funnel were placed the cyclic enone (15 mmol) and 1/5 pyridine-CH_2Cl_2 (17.5 mL). To this were added dropwise a solution of I_2 (1.5 eq, 15 mmol) in 17.5 mL of 1/5 pyridine CH_2Cl_2 over 1h. The mixture was stirred for an additional 14h, quenched with 50 mL of citric acid (6% aqueous solution), and extracted 2 times with CH_2Cl_2. The combined organic layers were washed with aqueous $Na_2S_2O_3$, 1M HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate)[6].

α-iodocyclohexenone.



167

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **167** was obtained in a 73% I.Y as a yellow solid. Substrate was already reported in *Angew. Chem. Int. Ed.* ***2013****, 52, 3208.*

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.77 (t, *J*=4 Hz, 1H), 2.59 (m, 2H), 2.44 (m, 2H), 2.09 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 192.35, 159.56, 104.02, 37.39, 30.07, 22.98. ^{13}C NMR (CD_3Cl, 100MHz): δ = 192.35, 159.56, 104.02, 37.39, 30.07, 22.98.

α-iodocyclopentenone.

168

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **168** was obtained in a 64% I.Y as abrown solid. Substrate was already reported in *Angew. Chem. Int. Ed.* ***2013****, 52, 3208.*

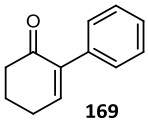
^{1}H NMR (CD_3Cl, 400MHz): δ = 8.01 (t, *J*= 4 Hz, 1H), 2.84 (m, 2H), 2.60 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 204.1, 169.7, 102.9, 31.3, 30.9. ^{13}C NMR (CD_3Cl, 100MHz): δ = 204.1, 169.7, 102.9, 31.3, 30.9.

6.4.2 General procedure for the Pd/C-catalyzed cross coupling of α-iodoenones with arylboronic acids

To a solution of α-iodoenone (1 mmol) in DME (3.5 mL) and H_2O (3.5 mL) were added Na_2CO_3 (2eq, 2 mmol), Aryl-$B(OH)_2$ (2 eq, 2 mmol) and 10% Pd/C. The mixture was stirred at 80ºC for 14h. Pd/C was filtered, and the filtrate was diluted with H_2O (3.5 mL) and extracted with Et_2O (3 times). The collected organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure[7].

Selected NMR data:

2-phenylcyclohex-2-enone.

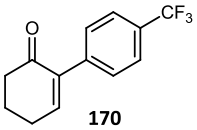


169

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **169** was obtained in a 47% I.Y as a white solid. Substrate was already reported in *Angew. Chem. Int. Ed.* ***2013****, 52, 3208-3212.*

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.42 (m, 5H), 7.03 (t, *J* = 4 Hz, 1H), 2.67 (m, 4H), 2.22 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 198.06, 148.07, 140.57, 136.70, 128.76, 128.13, 127.69, 39.22, 26.76, 23.08.

2-(4-trifluoromethyl)phenylcyclohex-2-enone.

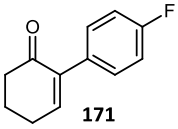


170

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **170** was obtained in a 52% I.Y as a yellowish solid. Substrate was already reported in Synlett. **2010**, *3*, 427.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.60 ppm (d, J = 8Hz, 2H), 7.42 (d, J = 8Hz, 2H), 7.11 (t, J = 4Hz, 1H), 2.60 (m, 4H), 2.13 (dt, J = 16Hz, 8Hz, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 197.89 ppm, 149.69, 139.42, 128.89, 126.94, 124.92, 115.34, 38.77, 26.27, 22.61. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -62.59 ppm (s).

2-(4-fluoro)phenylcyclohex-2-enone.

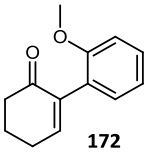


171

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **171** was obtained in a 51% I.Y as a brown solid. Substrate was already reported in Synlett. **2010**, *3*, 427.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.52 ppm (dd J = 8Hz, 4Hz, 2H), 7.26 (dd, J = 8Hz, 4Hz, 2H), 7.14 (t, J = 8Hz, 1H), 2.81 (m, 4H), 2.34 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 186.55 ppm, 148.33, 139.58, 129.89, 115.94, 114.60, 38.87, 26.33, 22.86. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -114.84 (dq, J = 11.3, 3.7 Hz).

2-(2-methoxy)phenylcyclohex-2-enone.

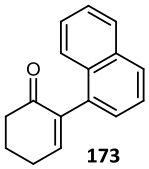


172

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **172** was purified in a 44% I.Y as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.29 (dt J = 8, 2Hz, 1H), 7.05 (dd, J = 8, 2Hz, 1H), 6.94 (t, J = 8Hz, 1H), 6.90 (m, 2H), 3.76 (s, 3H), 2.59 (dd, J = 8Hz, 2H), 2.52 (m, 2H), 2.13 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 197.54 ppm, 157.05, 147.89, 138.64, 130.44, 129.17, 126.49, 120.61, 110.77, 55.53, 38.41, 26.26, 22.98. HRMS ESI-TOF(m/z) = Calculated ($C_{13}H_{15}O_2$) 203.1072 ($M+H^+$) / Found 203.1062 ($M+H^+$)

2-(naphtalen-1-yl)cyclohex2-enone.

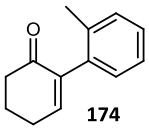


173

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **173** was purified in a 52% I.Y as a white solid. Substrate was already reported in *Tetrahedron* **2007**, *63*, 8449.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.84 ppm (t, J = 8Hz, 2H), 7.61 (d, J = 8Hz, 1H), 7.45 (m, 3H), 7.24 (d, J = 8Hz, 1H), 7.07 (t, J = 4Hz, 1H), 2.67 (m, 4H), 2.25 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 198.19 ppm, 150.09, 135.09, 133.45, 131.97, 128.33, 128.33, 127.02, 125.81, 125.66, 125.50, 125.25, 38.85, 26.53, 23.19

2-(2-methylphenyl)cyclohex-2-enone.

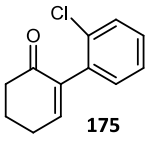


174

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **174** was obtained in a 69% I.Y as a colorless oil. Product already reported in *Angew. Chem. Int. Ed.* ***2013****, 52, 593-596.*

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.20 ppm (m, 3H), 7.03 (d, J = 8Hz, 1H), 6.90 (t, J = 4Hz, 1H), 2.60 (m, 2H), 2.54 (m, 2H), 2.16 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 197.83 ppm, 148.74, 141.66, 136.94, 136.48, 129.75, 129.51, 127.87, 125.62, 38.72, 26.35, 23.14, 20.002.

2-(2-chlorophenyl)cyclohex-2-enone.

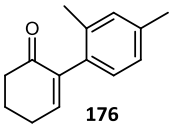


175

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **175** was obtained in a 56% I.Y. as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.31 (m, 1H), 7.18 (m, 2H), 7.06 (m, 1H), 6.87 (t, J = 4Hz, 1H), 2.54 (m, 2H), 2.48 (m, 2H), 2.08 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 197.02 ppm, 149.40, 139.74, 136.14, 133.37, 131.10, 129.33, 129.06, 126.56, 38.50, 26.26, 22.93. HRMS ESI-TOF(m/z) ($C_{12}H_{11}ClO$) = Calculated 207.0577 ($M+H^+$) / Found 207.0574 ($M+H^+$).

2-(2,4-dimethylphenyl)cyclohex-2-enone.

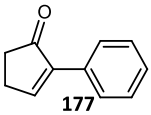


176

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **176** was obtained in a 82% I.Y. as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.01 ppm (m, 2H), 6.93 (s, 1H), 6.89 (t, J = 4Hz, 1H), 2.60 (m, 2H), 2.53 (m, 2H), 2.33 (s, 3H), 2.14 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 198.34 ppm, 148.76, 141.50, 137.34, 136.17, 130.60, 129.43, 126.19, 115.28, 38.70, 26.38, 23.15, 21.14, 19.93. HRMS ESI-TOF(m/z) ($C_{14}H_{16}O$) = Calculated 201.1279 ($M+H^+$) / Found 201.1275 ($M+H^+$).

2-phenylcyclopent-2-enone.

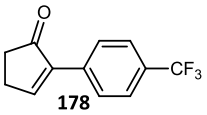


177

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **177** was obtained in a 51% I.Y as a light yellow oil. Substrate was already reported in *Angew. Chem. Int. Ed.* ***2013****, 52, 593-596.*

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.82 (d, J = 4 Hz, 1H), 7.69 (d, J = 7Hz, 2H), 7.36 (m, 3H), 2.71 (m, 2H), 2.62 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.6, 158.9, 143.4, 131.6, 128.4, 128.3, 127.0, 35.7, 26.2.

2-(4-(trifluoromethyl)phenyl)cyclopent-2-enone.

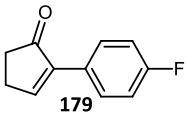


178

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **178** was obtained in a 24% I.Y. as a white solid. Substrate was already reported in *J. Am. Chem. Soc*. **2009**, *131*, 12886.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.93 ppm (t, J = 4Hz, 1H), 7.81 (d, J = 8Hz, 2H), 7.63 (d, J = 8Hz, 2H), 2.76 (m, 2H), 2.63 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.02 ppm, 160.53, 142.37, 135.01, 132.14, 132.04, 128.55, 128.47, 127.30, 125.36, 35.69, 26.38. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -62.72 (s).

2-(4-fluorophenyl)cyclopent-2-enone.

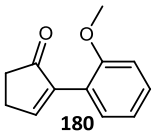


179

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **179** was obtained in a 62% I.Y. as a yellow oil. Substrate was already reported in *J. Am. Chem. Soc*. **2009**, *131*, 12886.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.79 ppm (t, J = 4Hz, 1H), 7.69 (d, J = 8Hz, 1H), 7.67 (d, J = 8Hz, 1H), 7.06 (t, J = 8Hz, 2H), 2.70 (m, 2H), 2.59 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.56 ppm, 162.57 (d , J = 250Hz), 158.68, 142,29, 128.80 (d, J = 8Hz), 127.71, 115.38 (d, J = 22Hz), 35.69, 26.14. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -113.11 ppm (dq, J = 11.3, 3.8Hz).

2-(2-methoxyphenyl)cyclopent-2-enone.

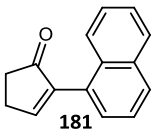


180

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **180** was obtained in a 36% I.Y. as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.97 ppm (t, J = 1.6Hz, 1H), 7.58 (dd, J = 8Hz, 4Hz, 1H), 7.29 (dt, J = 8Hz, 2Hz, 1H), 6.99 (dt, J = 8Hz, 4Hz, 1H), 6.93 (dd, J = 8Hz, 2Hz, 1H), 3.82 (s, 3H), 2.74 (m, 2H), 2.55 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ= 208.00 ppm, 162.17, 156.96, 140.54, 129.91, 129.21, 120.37, 110.91, 55.48, 34.83, 26.71. HRMS ESI-TOF(m/z) ($C_{12}H_{12}O_2$) = Calculated 211.0735 ($M+Na^+$) / Found 211.0731 ($M+Na^+$).

2-(naphthalen-1-yl)cyclopent-2-enone.

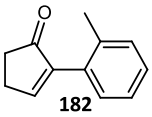


181

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **181** was obtained in a 42% I.Y. as a white solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.86 ppm (m, 3H), 7.81 (t, J = 4Hz, 1H), 7.49 (m, 3H), 7.39 (d, J = 8Hz, 1H), 2.88 (m, 2H), 2.71 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.77 ppm, 162.59, 144.93, 133.70, 131.38, 129.89, 128.63, 128.47, 126.89, 126.08, 125.87, 125.24, 125.14, 35.08, 27.06. HRMS ESI/TOF (m/z) ($C_{15}H_{12}O$) = Calculated 231.0786 ($M+Na^+$) / Found 231.0780 ($M+Na^+$)

2-(2-methyl)phenylcyclopentenone.

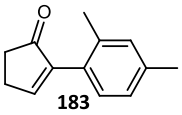


182

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **182** was obtained in a 23% I.Y. as a redish oil. Substrate was already reported in *J. Am. Chem. Soc*. **2009**, *131*, 12886.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.63 ppm (t, J = 4Hz, 1H), 7.24 (m, 4H), 2.79 (m, 2H), 2.61 (m, 2H), 2.26 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.70 ppm, 161.14, 146.25, 136.30, 131.81, 130.16, 129.26, 128.22, 125.67, 34.74, 26.88, 20.28.

2-(2,4-dimethylphenyl)cyclopent-2-enone.

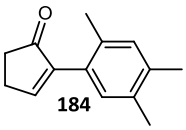


183

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **183** was obtained in a 59% I.Y. as a yellow solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.58 ppm (t, J = 4Hz, 1H), 7.04 (m, 3H), 2.76 (m, 2H), 2.58 (m, 2H), 2.32 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.83 ppm, 160.83, 146.12, 138.00, 135.97, 131.09, 129.18, 128.83, 126.31, 34.78, 26.82, 21.14, 20.19. HRMS ESI/TOF (m/z) ($C_{13}H_{14}O$) = Calculated ($C_{13}H_{14}O$) 209.0942 ($M+Na^+$) / Found 209.0939 ($M+Na^+$).

2-(2,4,5-trimethylphenyl)cyclopent-2-enone.

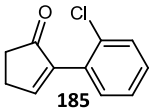


184

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **184** was obtained in a 65% I.Y. as a yellow oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.57 ppm (t, J = 4Hz, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 2.76 (m, 2H), 2.58 (m, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.17 (s,3H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.94 ppm, 160.71, 146.20, 136.57, 133.62, 133.40, 131.68, 130.40, 129.13, 34.79, 26.82, 19.64, 19.42, 19.19. HRMS ESI/TOF (m/z) ($C_{14}H_{16}O$) = Calculated 223.1099 ($M+Na^+$) / Found 223.1099 ($M+Na^+$)

2-(2-chloro)phenylcyclopentenone.

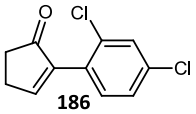


185

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **185** was obtained in a 28% I.Y. as a white crystalline solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.86 ppm (t, J = 4Hz, 1H), 7.42 (m, 1H), 7.32 (m, 1H), 7.27 (m, 2H), 2.79 (m, 2H), 2.58 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 206.85 ppm, 162.93, 142.91, 132.93, 130.88, 130.72, 129.84, 129.29, 126.57, 34.66, 26.86. HRMS ESI-TOF(m/z) ($C_{11}H_9ClO$) = Calculated 193.0420 ($M+H^+$) / Found 193.0405 ($M+H^+$).

2-(2,4-dichlorophenyl)cyclopent-2-enone.

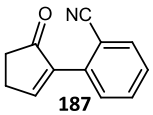


186

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **186** was obtained in a 48% I.Y. as a yellow oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.86 ppm (t, J = 4Hz, 1H), 7.26 (m, 3H), 2.77 (m, 2H), 2.56 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 206.61 ppm, 163.19, 141.75, 134.46, 131.91, 131.41, 129.67, 126.96, 34.57, 26.89. HRMS ESI/TOF (m/z) ($C_{11}H_8Cl_2O$) = Calculated 227.0030 ($M+H^+$) / Found 227.0030 ($M+H^+$)

2-(2-cyano)phenylcyclopentenone.



187

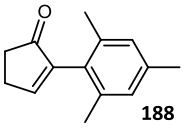
This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **187** was obtained in a 26% I.Y. as a light purple solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 8.13 ppm (t, J = 4Hz, 1H), 7.73 (d, J = 8Hz, 1H), 7.63 (m 2H), 7.43 (m, 1H), 2.85 (m, 2H), 2.65 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 206.35 ppm, 163.65, 141.34, 135.12, 133.50, 132.60, 129.60, 128.40, 118.31, 111.14, 34.90, 26.89. HRMS ESI/TOF (m/z) ($C_{12}H_9NO$) = Calculated 206.0582 ($M+Na^+$) /Found 206.0579 ($M+Na^+$)

6.4.3 General experimental procedure for the synthesis of 2-mesitylcyclopent-2-enone

Pd-Xphos G3 (0.025 mmol), K_3PO_4 (1.5 mmol), mesitylboronic acid (0.55 mmol) and α-iodoenone (0.5 mmol) were added into a previously dried schlenck tube under argon. Afterwards, dry toluene (3 mL) was added and the whole solution started stirring. Finally, the reaction vessel was heated up to 110ºC and left overnight. Afterwards, the reaction was quenched with Et_2O and water, the organic phases were collected, dried over $MgSO_4$ and concentrated under reduced pressure[8].

2-mesitylcyclopent-2-enone:



188

This product was purified by flash chromatography silica gel (8:1 (Petroleum ether: Ethyl acetate). Product **188** was obtained in a 30% I.Y. as a brown solid.

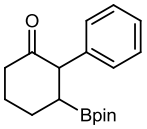
^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.63 (t, J = 4Hz, 1H), 6.99 (s, 2H), 2.79 (m, 2H), 2.61 (m, 2H), 2.26 (s, 3H), 2.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 207.70, 161.14, 146.25, 136.30, 131.81, 130.16, 129.26, 128.22, 125.67, 34.74, 26.88, 20.28. HRMS (ESI-TOF) m/z ($C_{14}H_{16}O$): Calculated 201.1279 ($M+H^+$); Found 201.1283 ($M+H^+$).

6.4.4 General procedure for the Cu-catalyzed β-boration of α-aryl enones

CuCl (0.0075 mmols), PCy_3 (0.015 mmols), NaOtBu (0.0225 mmols) and B_2pin_2 (0.275 mmols) were added into a previously dried schlenck tube under argon. THF (2mL) was then added and the whole solution was left stirring for 5 minutes. Then, alpha-aryl ketone (0.25 mmol) was introduced into the stirring solution. Finally, MeOH (0.625 mmols) was added. The reaction was left stirring overnight. Conversion was determined by ^{1}H NMR and GC analysis[9].

Selected NMR data:

2-phenyl-3-pinacolboryl cyclohexanone.

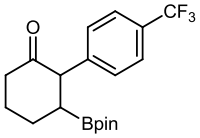


169b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **169b** was obtained in a 63% I.Y as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.34 ppm (d, J = 8Hz, 2H), 7.27 ppm (m, 3H), 3.80 ppm (d, J = 12Hz, 1H), 2.48 (m, 1H), 2.31 (m, 1H), 2.09 (m, 2H), 1.91 (m, 3H), 1.16 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.75 ppm, 138.37, 128.97, 128.07, 126.56, 83.57, 57.21, 39.38, 26.93, 25.13, 24.72, 24.59. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.08 ppm. HRMS ESI-TOF(m/z) = Calculated ($C_{18}H_{25}BNaO_3$) 323.1794 ($M+Na^+$) / 323.1790 ($M+Na^+$)

2-(4-trifluoromethyl-phenyl)-3-pinacolboryl cyclohexanone.

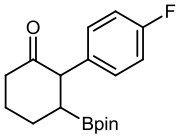


170b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **170b** was obtained in a 64% I.Y as a brown solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.54 ppm (d, J = 8Hz, 2H), 7.47 (d, J = 8Hz, 2H), 3.80 (d, J = 12Hz, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 2.05 (m, 3H), 1.97 (m, 2H), 1.18 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 209.07 ppm, 142.55, 129.49, 124.99, 83.75, 57.26, 40.63, 26.49, 26.07, 24.69. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -62.51 ppm (s). ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.20 ppm. HRMS ESI-TOF(m/z) = Calculated ($C_{19}H_{25}BF_3O_3$) 369.1849 ($M+H^+$) / Found 369.1854 ($M+H^+$).

2-(4-fluorophenyl)-3-pinacolboryl cyclohexanone.

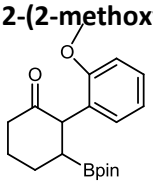


171b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **171b** was obtained in a 70 % I.Y as a yellow oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.31 ppm (m, 2H), 6.93 (m, 2H), 3.75 (d, J = 12Hz, 1H), 2.48 (m, 1H), 2.33 (m, 1H), 2.05 (m, 3H), 1.94 (m, 2H), 1.17 (s, 6H), 1.11 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.33 ppm, 133.96, 130.55, 116.12, 114.84, 83.59, 56.47, 40.27, 26.75, 25.68, 24.73, 24.63. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = - 116.33 (dq, J = 11.3, 3.77 Hz). ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.85 ppm. HRMS ESI-TOF(m/z) = Calculated ($C_{18}H_{25}BFO_3$) 319.1881 ($M+H^+$) / Found 319.1870 ($M+H^+$).

2-(2-methoxyphenyl)-3-pinacolboryl cyclohexanone.

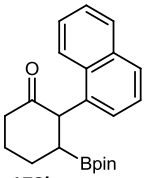


172b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **172b** was obtained in a 47 % I.Y as a yellow oil. Product was obtained as a diaestereomeric mixture of products (50/50).

Diaestereomer anti: ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.51 ppm (d, J = 8Hz, 1H), 7.19 (t, J = 8Hz, 1H), 6.90 (t, J = 8Hz, 1H), 6.82 (d, J= 8Hz, 1H), 4.17 (d, J = 12Hz, 1H), 3.77 (s, 3H), 2.47 (m, 2H), 2.03 (m, 2H), 1.17 (s, 6H), 1.13 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 209.55 ppm, 157.01, 130.08, 127.67, 119.87, 110.14, 83.29, 55.20, 50.07, 41.29, 27.11, 26.15, 24.64. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.65 (s). HRMS ESI-TOF(m/z) = Calculated ($C_{19}H_{28}BO_4$) 331.2081 ($M+H^+$) / Found 331.2076 ($M+H^+$) *Diaestereomer syn:* ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.20 ppm (t, J = 8Hz, 1H), 7.09 (d, J = 8Hz, 1H), 6.90 (t, J = 8Hz, 1H), 6.83 (d, J = 8Hz, 1H), 4.02 (d, J = 4Hz, 1H), 2.52 (m, 2H), 1.89 (m, 5H), 1.00 (s, 6H), 0.96 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.66 ppm, 157.37, 129.86, 128.15, 127.82, 120.55, 110.70, 83.42, 55.66, 51.99, 42.49, 29.92, 29.77, 27.61, 24.96, 24.64, 24.45. ^{11}B NMR (CD_3Cl, 128MHz): δ = 32.91 (s). HRMS ESI-TOF(m/z) = Calculated ($C_{19}H_{28}BO_4$) 331.2081 ($M+H^+$) / Found 331.2076 ($M+H^+$)

2-(naphtalen-1-yl)-3-pinacolboryl cyclohexanone.

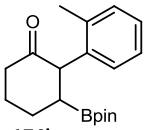


173b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **173b** was obtained in a 76 % I.Y as a brownish solid.

^{1}H NMR (CD_3Cl, 400MHz): δ 8.10 ppm (d, J = 8Hz, 1H), 7.82 (t, J = 8Hz, 2H), 7.74 (d, J = 8Hz, 1H), 7.48 (m, 3H), 4.56 (d, J = 12Hz, 1H), 2.59 (m, 1H), 2.37 (m, 2H), 2.18 (m, 4H), 1.14 (s, 6H), 1.02 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.44 ppm, 134.54, 113.84, 132.27, 128.77, 127.59, 126.19, 126.11, 125.35, 124.89, 123.73, 83.51, 52.90, 40.55, 27.60, 26.34, 24.62. ^{11}B NMR (CD_3Cl, 128MHz): δ = 36.36 ppm. HRMS ESI-TOF(m/z) = Calculated ($C_{22}H_{27}BNaO_3$) 373.1951 ($M+Na^+$) / Found 373.1948 ($M+Na^+$).

2-(o-tolyl)-3-pinacolboryl cyclohexanone.

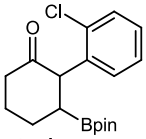


174b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **174b** was obtained in a 66% I.Y as a yellowish oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.55 ppm (d, J = 4Hz, 1H), 7.11 (m, 3H), 3.93 (d, J = 12Hz, 1H), 2.59 (m, 3H), 2.40 (m, 2H), 2.29 (s, 3H), 2.06 (m, 2H), 1.14 (s, 6H), 1.07 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 209.92 ppm, 137.32, 136.81, 130.27, 128.66, 126.72, 125.47, 83.42, 53.32, 40.78, 26.69, 26.47, 24.63, 19.95. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.25 ppm (s). HRMS ESI-TOF(m/z) ($C_{19}H_{27}BO_3$) = Calculated 315.2132 ($M+H^+$) / Found 315.2127 ($M+H^+$).

2-(2-chlorophenyl)-3-pinacolboryl cyclohexanone.

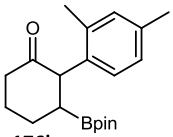


175b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **175b** was obtained in a 21% I.Y as a white oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.34 (m, 4H), 4.23 (d, J = 12Hz, 1H), 2.55 (m, 3H), 2.25 (m, 2H), 1.96 (m, 2H), 1.00 (s, 6H), 0.96 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 209.42 ppm, 136.55, 131.15, 129.43, 129.23, 128.03, 126.50, 83.43, 54.66, 42.44, 29.71, 25.02, 24.15, 22.77, 14.12. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.56 (s). HRMS ESI-TOF(m/z) ($C_{18}H_{24}BClO_3$) = Calculated 357.1405 ($M+Na^+$) / Found 357.1405 ($M+Na^+$).

2-(2,4-dimethylphenyl)-3-pinacolboryl cyclohexanone.



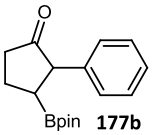
176b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **176b** was obtained in a 67% I.Y as a colorless oil. Product was obtained as a diaestereomeric mixture of products (63/37).

Diaestereomer *anti*: ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.23 (m, 1H), 6.97 (s, 1H), 6.80 (d, J = 8Hz, 1H), 3.89 (d, J = 12Hz, 1H), 2.54 (m, 2H), 2.34 (m, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.10 (m, 2H), 1.16 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.40 ppm, 136.09, 134.14, 131.27, 129.56, 126.18, 120.43, 115.30, 83.52, 53.36, 40.76, 27.48, 26.55, 24.67, 20.92, 19.83. ^{11}B

NMR (CD_3Cl, 128MHz): δ = 33.34 ppm (s). HRMS ESI-TOF(m/z) ($C_{20}H_{29}BO_3$) = Calculated 346.2553 ($M+NH_4^+$) / Found 346.2549 ($M+NH_4^+$). Diaestereomer *syn*: ^1H NMR (CD_3Cl, 400MHz): δ = 7.23 (m, 1H), 6.92 (s, 1H), 6.80 (d, J = 8Hz, 1H), 3.85 (d, J = 4Hz, 1H), 2.54 (m, 2H), 2.34 (m, 3H), 2.25 (s, 3H), 2.20 (s, 3H), 2.10 (m, 2H), 0.96 (s, 6H), 0.95(s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 210.40 ppm, 136.65, 133.77, 130.79, 128.45, 126.52, 120.45, 115.30, 83.30, 53.74, 42.59, 27.62, 26.76, 24.10, 20.92, 19.86. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.34 ppm (s). HRMS ESI-TOF(m/z) ($C_{20}H_{29}BO_3$) = Calculated 346.2553 ($M+NH_4^+$) / Found 346.2549 ($M+NH_4^+$).

2-phenyl-3-pinacolboryl cyclopentanone.

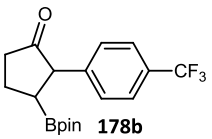


177b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) as a diaestereomeric mixture of products (70/30). Product **177b** was obtained in a 60% I.Y as a white solid.

Diaestereomer anti: ^1H NMR (CD_3Cl, 400MHz): δ = 7.25 ppm (m, 5H), 3.58 (d, J = 12Hz, 1H), 2.53 (m, 1H), 2.36 (m, 1H), 2.18 (m, 3H), 10.3 (s, 6H), 0.97 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 219.53 ppm, 138.88, 128.85, 128.24, 126.75, 83.34, 55.83, 38.43, 24.76, 24.50, 23.27. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.41 (s). HRMS ESI-TOF(m/z) ($C_{17}H_{23}BO_3$) = Calculated 309.1638 ($M+Na^+$) / Found 309.1635 ($M+Na^+$) *Diaestereomer syn:* ^1H NMR (CD_3Cl, 400MHz): δ = 7.25 ppm (m, 5H), 3.37 (d, J = 4Hz, 1H), 2.53 (m, 1H), 2.36 (m, 1H), 2.18 (m, 3H), 1.18 (s, 12H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 218.81 ppm, 138.54, 128.85, 128.24, 126.75, 83.55, 58.04, 39.09, 24.76, 24.57, 23.06. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.41 (s). HRMS ESI-TOF(m/z) ($C_{17}H_{23}BO_3$) = Calculated 309.1638 ($M+Na^+$) / Found 309.1635 ($M+Na^+$)

2-(4-(trifluoromethyl)phenyl)-3-pinacolboryl cyclopentanone.



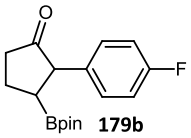
178b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) Product **178b** was obtained in a 25% I.Y as a colorless oil.

^1H NMR (CD_3Cl, 400MHz): δ = 7.56 ppm (d, J = 8Hz, 2H), 7.28 (d, J = 8Hz, 2H), 3.43 (d, J = 12Hz, 1H), 2.55 (dd, J = 12Hz, 8Hz, 1H), 2.30 (m, 2H), 1.87 (m, 2H), 1.19 (s, 12H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 217.74 ppm, 142.51, 128.83, 125.35, 83.73, 57.69, 38.97, 29.69, 24.75, 24.56,

23.06. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -62.49 (s). ^{11}B NMR (CD_3Cl, 128MHz): δ = 35.62 (s). HRMS ESI/TOF (m/z) ($C_{18}H_{22}BF_3O_3$) = Calculated 377.1512 ($M+Na^+$) / Found 377.1511 ($M+Na^+$).

2-(4-fluorophenyl)-3-pinacolboryl cyclopentanone.

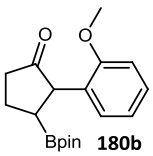


179b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) Product **179b** was obtained in a 70% I.Y as a colorless oil. The product **179b** was obtained as a diaestereomeric mixture (83/17) of products.

Diaestereomer anti: ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.21 ppm (d, J = 8Hz, 1H), 7.19 (d, J = 8Hz, 1H), 6.96 (t, J = 8Hz, 2H), 3.54 (d, J = 12Hz, 1H), 2.52 (m, 1H), 2.39 (m, 1H), 2.21 (m, 1H), 2.15 (m, 2H), 1.04 (s, 6H), 0.99 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 219.04 ppm, 161.89 (d, J = 247Hz), 134.56, 130.43 (d, J = 8Hz), 115.05 (d, J = 21Hz), 83.42, 55.11, 38.19, 29.68, 24.76, 24.49, 23.10. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -116.17 ppm (dq, J = 11.3, 3.8Hz) ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.20 ppm (s). HRMS ESI/TOF (m/z) ($C_{17}H_{22}BFO_3$) = Calculated 327.1544 ($M+Na^+$) / Found 327.1543 ($M+Na^+$). *Diaestereomer syn*: ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.13 ppm (d, J = 8Hz, 1H), 7.11 (d, J = 8Hz, 1H), 6.96 (t, J = 8Hz, 2H), 3.34 (d, J = 4Hz, 1H), 2.52 (m, 1H), 2.39 (m, 1H), 2.21 (m, 1H), 2.15 (m , 2H), 1.18 (s, 6H), 1.17 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 218.46 ppm, 161.89 8d, J = 247Hz), 134.05, 129.94 (d, J = 8Hz), 115.25 (d, J = 21Hz), 83.64, 57.25, 38.86, 29.35, 24.73, 24.56, 22.93. ^{19}F NMR (CD_3Cl, 376.8 MHz): δ = -116.35 (dq, J = 11.3, 3.8Hz). ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.20 ppm (s). HRMS ESI/TOF (m/z) ($C_{17}H_{22}BFO_3$) = Calculated 327.1544 ($M+Na^+$) / Found 327.1543 ($M+Na^+$).

2-(2-methoxyphenyl)-3-pinacolboryl cyclopentanone.



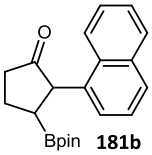
180b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **180b** was obtained in a 70 % I.Y as a pale yellow oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.13 ppm (d, J = 8Hz, 2H), 6.84 (t, J = 8Hz, 1H), 6.76 (d, J = 8Hz, 1H), 3.75 (s, 3H), 3.72 (d, J = 12Hz, 1H), 2.54 (m, 1H), 2.39 (m, 1H), 2.24 (m, 2H), 2.06 (m, 1H), 0.97 (s, 6H), 0.90 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 220.71 ppm, 157.06, 131.12, 128.55, 128.06, 120.42, 110.65, 83.00, 55.21, 50.91, 39.16, 24.76, 24.51, 23.66. ^{11}B NMR (CD_3Cl,

128MHz): δ = 36.00 (s). HRMS ESI-TOF(m/z) ($C_{18}H_{25}BO_4$) = Calculated 317.1924 ($M+H^+$) / Found 317.1936 ($M+H^+$).

2-(naphthalen-1-yl)-3-pinacolboryl cyclopentanone.

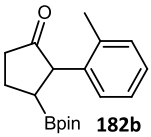


181b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **181b** was obtained in a 86 % I.Y as a white solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 8.03 ppm (d, J = 8Hz, 1H), 7.82 (d, J = 8Hz, 1H), 7.72 (d, J = 8Hz, 1H), 7.52 (t, J = 8Hz, 1H), 7.46 (t, J = 8Hz, 1H), 7.39 (t, J = 8Hz, 1H), 7.33 (d, J = 8Hz), 4.32 (d, J = 12Hz, 1H), 2.70 (dt, J = 16, 8Hz, 1H), 2.54 (t, J = 8Hz, 1H), 2.48 (m, 1H), 2.24 (q, J = 8Hz, 2H), 0.90 (s, 6H), 0.78 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 219.88 ppm, 135.14, 133.84, 132.54, 128.65, 127.46, 126.06, 125.88, 125.48, 125.15, 123.68, 83.17, 51.85, 38.82, 24.58, 24.42, 23.26. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.72 (s). HRMS ESI/TOF (m/z) ($C_{21}H_{25}BO_3$) = Calculated 359.1794 ($M+Na^+$) / Found 359.1798 ($M+Na^+$).

2-(2-methylphenyl)-3-pinacolboryl cyclopentanone.

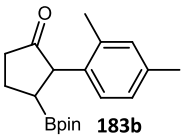


182b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **182b** was obtained in a 49 % I.Y as a white crystalline solid.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.08 ppm (m, 4H), 3.73 (d, J = 12Hz, 1H), 2.60 (dt, J = 20, 12Hz, 1H), 2.42 (m, 1H), 2.35 (s, 3H), 2.30 (m, 1H), 2.15 (m, 2H), 1.01 (s, 6H), 0.91 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 220.65 ppm, 137.80, 137.12, 130.17, 128.21, 126.72, 125.89, 83.24, 52.40, 38.78, 24.80, 24.45, 23.23, 20.06. ^{11}B NMR (CD_3Cl, 128MHz): δ = 32.69 ppm (s). HRMS ESI-TOF(m/z) ($C_{18}H_{25}BO_3$) = Calculated 301.1975 ($M+H^+$) / Found 301.1977 ($M+H^+$).

2-(2,4-dimethylphenyl)-3-pinacolboryl cyclopentanone.

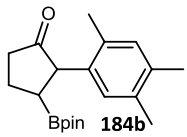


183b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) as a diaestereomeric mixture of products (80/20). Product **183b** was obtained in a 65% I.Y as a colorless oil.

Diaestereomer anti: ^{1}H NMR (CD_3Cl, 400MHz): δ = 6.93 ppm (m, 3H), 3.70 (d, J = 12Hz, 1H), 2.58 (m, 1H), 2.41 (m, 2H), 2.30 (s, 3H), 2.23 (s, 3H), 2.13 (m, 2H), 1.02 (s, 6H), 0.93 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 220.71 ppm, 136.90, 136.16, 134.72, 130.92, 128.08, 126.46, 83.21, 52.30, 38.67, 25.00, 24.77, 24.48, 23.21, 20.90, 19.98. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.38 ppm (s). HRMS ESI/TOF (m/z) ($C_{19}H_{27}BO_3$) = Calculated 337.1951 ($M+Na^+$) / Found 337.1957 ($M+Na^+$). *Diaestereomer syn*: ^{1}H NMR (CD_3Cl, 400MHz): δ = 6.93 (m, 3H), 3.56 (d, J = 4Hz, 1H), 2.58 (m, 1H), 2.41 (m, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.13 (m, 2H), 1.16 (s, 6H), 1.15 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 219.50 ppm, 136.53, 136.12, 134.22, 131.25, 127.92, 126.75, 83.51, 55.26, 38.89, 25.00, 24.71, 24.60, 23.26, 20.96, 19.96. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.38 ppm (s). HRMS ESI/TOF (m/z) ($C_{19}H_{27}BO_3$) = Calculated 337.1951 ($M+Na^+$) / Found 337.1957 ($M+Na^+$).

2-(2,4,5-trimethylphenyl)-3-pinacolboryl cyclopentanone.

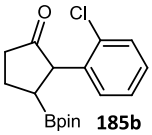


184b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) as a diaestereomeric mixture of products (86/14). Product **184b** was obtained in a 65% I.Y as a colorless oil.

Diaestereomer anti: ^{1}H NMR (CD_3Cl, 400MHz): δ = 6.87 ppm (s, 1H), 6.81 (s, 1H), 3.67 (d, J = 12Hz, 1H), 2.61 (m, 1H), 2.40 (m, 1H), 2.26 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.12 (m, 3H), 1.02 (s, 6H), 0.93 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 220.75 ppm, 134.78, 134.71, 134.29, 133.39, 131.49, 129.33, 83.14, 52.53, 38.64, 24.76, 24.43, 23.25, 19.41, 19.38, 19.21. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.48 ppm (s). HRMS ESI/TOF (m/z) ($C_{20}H_{29}BO_3$) = Calculated 351.2107 ($M+Na^+$) / Found 351.2107 ($M+Na^+$). *Diaestereomer syn*: ^{1}H NMR (CD_3Cl, 400MHz): δ = 6.90 (s, 1H), 6.69 (s, 1H), 3.53 (d, J = 4Hz, 1H), 2.61 (m, 1H), 2.40 (m, 1H), 2.26 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.12 (m, 3H), 1.17 (s, 6H), 1.16 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 220.75 ppm, 134.78, 134.71, 134.58, 133.82, 131.81, 129.44, 83.51, 55.32, 39.04, 24.76, 24.43, 23.32, 19.41, 19.38, 19.21. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.48 ppm (s). HRMS ESI/TOF (m/z) ($C_{20}H_{29}BO_3$) = Calculated 351.2107 ($M+Na^+$) / Found 351.2107 ($M+Na^+$).

2-(2-chlorophenyl)-3-pinacolboryl cyclopentanone:

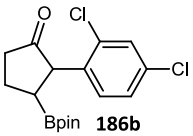


185b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1) as a diaestereomeric mixture of products (83/17). Product **185b** was obtained in a 53 % I.Y as a white crystalline solid.

Diaestereomer anti: ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.32 ppm (d, J = 8Hz, 1H), 7.26 (dd, J = 8, 4Hz, 1H), 7.15 (m, 2H), 3.97 (d, J = 12Hz), 2.60 (m, 1H), 2.47 (m, 2H), 2.12 (m, 2H), 1.05 (s, 6H), 0.94 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 218.47 ppm, 136.56, 135.15, 130.51, 129.18, 128.09, 126.47, 83.32, 53.83, 38.35, 24.86, 24.42, 23.00. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.86 ppm (s). HRMS ESI-TOF(m/z) ($C_{17}H_{22}BClO_3$) = Calculated 321.1429 ($M+H^+$) / Found 321.1420 ($M+H^+$) *Diaestereomer syn:* ^{1}H NMR (CD_3Cl, 400MHz): δ = 7.34 ppm (m, 1H), 7.15 (m, 3H), 3.69 (d, J = 4Hz, 1H), 2.47 (m, 2H), 2.25 (m, 1H), 2.07 (td, J = 12, 4Hz), 1.93 (m, 1H), 1.18 (s, 6H), 1.17 (s, 6H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 217.85 ppm, 136.69, 133.89, 131.21, 129.91, 128.32, 126.78, 83.58, 57.06, 38.50, 29.67, 24.80, 24.57, 23.45. ^{11}B NMR (CD_3Cl, 128MHz): δ = 36.00 ppm (s). HRMS ESI-TOF(m/z) ($C_{17}H_{22}BClO_3$) = Calculated 321.1429 ($M+H^+$) / Found 321.1420 ($M+H^+$)

2-(2,4-dichlorophenyl)-3-pinacolboryl cyclopentanone:

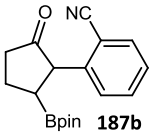


186b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1)). Product **186b** was obtained in a 48% I.Y as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.36 ppm (d, J = 4Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.05 (d, J = 8Hz, 1H), 3.66 (d, J = 12Hz, 1H), 2.44 (m, 2H), 2.25 (m, 1H), 1.97 (m, 2H), 1.18 (s, 12H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 217.24 ppm, 135.43, 134.51, 133.43, 131.92, 129.63, 127.04, 83.65, 56.48, 38.37, 29.68, 24.80, 24.59, 23.36. ^{11}B NMR (CD_3Cl, 128MHz): δ = 34.20 ppm (s). HRMS ESI/TOF (m/z) ($C_{17}H_{21}BCl_2O_3$) = Calculated 355.1039 ($M+H^+$) / Found 355.1044 ($M+H^+$)

2-(2-cyanophenyl)-3-pinacolboryl cyclopentanone:



187b

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 8:1). Product **187b** was obtained in a 62 % I.Y. as a yellow oil.

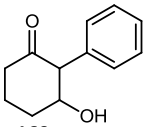
^{1}H NMR (CD_3Cl, 400MHz): δ = 7.64 ppm (d, J = 8Hz, 1H), 7.52 (t, J = 8Hz, 1H), 7.33 (t, J = 8Hz, 1H), 7.21 (d, J = 8Hz, 1H), 3.68 (d, J = 12Hz, 1H), 2.50 (m, 2H), 2.29 (m, 1H), 1.97 (m, 2H), 1.26 (s, 6H), 1.17 (s, 6H) ^{13}C NMR (CD_3Cl, 100MHz): δ = 216.78 ppm, 142.59, 133.19, 132.73, 129.70, 127.38, 118.15, 113.11, 83.79, 83.07, 57.64, 38.61, 29.71, 25.31, 24.75, 24.51, 23.21. ^{11}B NMR (CD_3Cl, 128MHz): δ = 33.95 ppm (s). HRMS ESI/TOF (m/z) ($C_{18}H_{22}BNO_3$) = Calculated 334.1590 ($M+Na^+$) / Found 334.1592 ($M+Na^+$)

6.4.5 General procedure for the oxidation of 3-pinacolboryl-2-aryl-cyclohexenones

A solution of, 2N NaOH/32% H_2O_2 (2:1 v/v 1mL) was added dropwise to a solution of α-aryl β-boryl cycloenone (0.1 mmol) in THF/Et_2O (1:1 v/v, 3mL) at 0ºC under vigorous stirring. The reaction mixture was kept at 0ºC and stirring for 30 more minutes. Afterwards, Et_2O was added and the phases were separated. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated and purified by column chromatography.

Selected NMR data:

3-hydroxy-2-phenylcyclohexanone

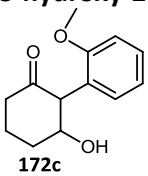


169c

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 4:1). Product **169c** was obtained in a 93% I.Y as a colorless oil.

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.38 ppm (m, 3H), 7.17 (d, J = 8Hz, 2H), 4.01 (dt, J = 12Hz, 4Hz, 1H), 3.57 (d, J = 12Hz, 1H), 2.42 (m, 2H), 2.14 (m, 1H), 1.88 (m, 1H), 1.72 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 207.27 ppm, 134.45, 129.69, 128.73, 127.79, 74.55, 66.85, 40.90, 32.81, 20.67. HRMS ESI-TOF(m/z) = Calculated ($C_{12}H_{15}O_2$) 191.1072 ($M+H^+$) / Found 191.1070 ($M+H^+$)

3-hydroxy-2-(2-methoxyphenyl)cyclohexanone.



172c

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 4:1). Product **172c** was obtained in a 90% I.Y as a colorless oil.

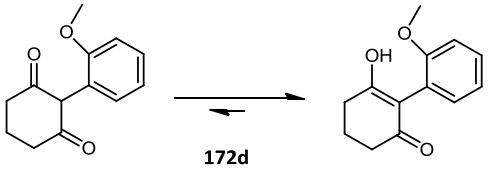
^{1}H NMR (CD_3Cl, 400MHz): δ = 7.45 ppm (dd, J = 8Hz, 4Hz, 1H), 7.29 (dt, J = 8Hz, 4Hz, 1H), 7.00 (dt, J = 8Hz, 4Hz, 1H), 6.92 (dd, J = 8Hz, 4Hz, 1H), 4.38 (m, 1H), 4.27 (d, J = 4Hz, 1H), 3.81 (s, 3H), 2.51 (m, 3H), 2.34 (m, 2H), 2.02 (m, 2H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 208.24 ppm, 156.92, 131.24, 128.51, 124.33, 120.67, 110.88, 73.06, 56.24, 55.57, 55.30, 41.85, 30.06, 20.75. HRMS ESI-TOF(m/z) = Calculated ($C_{13}H_{17}O_3$) 221.1178 ($M+H^+$) / Found 221.1165 ($M+H^+$)

6.4.6 General procedure for the oxidation of 3-hydroxy-2-aryl-cyclohexenone

To a solution of crude alcohol (5 mmol) in DCM (2mL) was added 200 mg of activated 3A molecular sieves. The solution was cooled to 0ºC and Pyridinium Chlorochromate (PCC) (1.25 mmol) was added portionwise over 5 min. The solution was left stirring for 1h at 0ºC and then left at r.t overnight. Afterwards, the reaction was quenched with DCM (2mL) and Et_2O (2mL), and the contents of the flask were filtered over a pad of Celite. The filtrate was then concentrated under vacuo and purified by column chromatography[10].

Selected NMR data:

2(2-methoxyphenyl)-1,3-cyclohexanedione.



172d

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 4:1). Product **172d** was obtained in a 23% I.Y as a dark-yellow solid (Enol form)

^{1}H NMR (CD_3Cl, 400MHz): δ = 7.60 ppm (dd, J = 8Hz, 4Hz, 1H), 7.39 (td, J = 8, 4Hz, 1H), 7.10 (td, J = 8, 4Hz, 1H), 6.87 (dd, J = 8, 4Hz, 1H), 3.71 (s, 3H), 3.07 (m, 2H), 2.76 (m, 2H), 2.23 (m, 1H), 2.04 (m, 1H). ^{13}C NMR (CD_3Cl, 100MHz): δ = 199.90 ppm, 160.17, 154.64, 130.37, 129.26, 124.14, 121.31, 110.84, 55.52, 36.71, 29.72, 17.49. HRMS ESI-TOF(m/z) = Calculated ($C_{13}H_{15}O_3$) 219.1021 ($M+H^+$) / Found 219.1019 ($M+H^+$)

6.4.7 General procedure for the oxidation of 3-pinacolboryl-2-aryl-cyclopentanones.

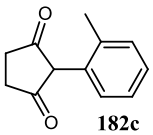
A solution of, 2N NaOH/32% H_2O_2 (2:1 v/v 1mL) was added dropwise to a solution of α-aryl β-boryl cycloenone (0.1 mmol) in THF/Et_2O (1:1 v/v, 3mL) at 0ºC under vigorous stirring. The reaction mixture was kept at 0ºC and stirring for 30 more minutes. Afterwards, Et_2O was added and the phases were separated. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated and purified by column chromatography.

6.4.8 General procedure for the one-pot transformation of α-iodo-cyclopentenone to 2-aryl-1,3-cyclopentane-diones.

To a solution of α-iodoenone (0.5 mmol) in DME (4 mL) and H_2O (4 mL) were added Na_2CO_3 (2eq, 1mmol), Aryl-$B(OH)_2$ (1.1 eq, 0.55 mmol) and 10% Pd/C. The mixture was stirred at 80ºC for 14h. Pd/C was filtered, and the filtrate was diluted with H_2O (3.5 mL) and extracted with Et_2O (3 times). The collected organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Afterwards, CuCl (0.015 mmols), PCy_3 (0.03 mmols), NaOtBu (0.045 mmols) and B_2pin_2 (0.55 mmols) were added into a previously dried schlenck tube under argon. THF (3mL) was then added and the whole solution was left stirring for 5 minutes. Then, the crude of the alpha-aryl ketone (0.5 mmol) was introduced into the stirring solution. Finally, MeOH (1.25 mmols) was added. The reaction was left stirring overnight. Afterwards, a solution of, 2N NaOH/32% H_2O_2 (2:1 v/v 3.3mL) was added dropwise to the solution of α-aryl β-boryl cycloenone (0.5 mmol) in THF/Et_2O (1:1 v/v, 3mL: 3mL) at 0ºC under vigorous stirring. The reaction mixture was kept at 0ºC and stirring for 1 hour. Afterwards, Et_2O was added and the phases were separated. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$ and concetrated. Conversion was determined by ^{1}H NMR and GC analysis[11].

Selected NMR data:

2-(2-methylphenyl)cyclopentane-1,3-dione.

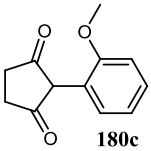


182c

This product was purified by column chromatography (silica gel, petroleum ether: ethyl acetate 6:1). Product **182c** was obtained in a 32% I.Y.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.30 (m, 2H), 7.21 (m, 2H), 3.99 (s, 1H), 2.50 (m, 2H), 2.30 (m, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.56, 137.00, 129.85, 128.80, 128.13, 125.60, 64.94, 31.47, 22.58, 19.63. HRMS (ESI-TOF) m/z ($C_{12}H_{12}O_2$): Calculated 189.0916 ($M+H^+$) / Found 189.0913 ($M+H^+$)

2-(2-methoxyphenyl)cyclopentane-1,3-dione.

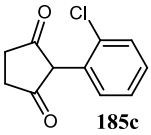


180c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 4:1). Product **180c** was obtained in 34% isolated yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.33 (m, 2H), 6.98 (t, J = 8Hz, 1H), 6.90 (d, J = 8Hz, 1H), 3.88 (s, 1H), 3.80 (s, 3H), 2.35 (m, 4H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 207.65, 157.73, 130.14, 128.14, 120.61, 119.26, 110.09, 65.38, 55.55, 31.17, 22.30. HRMS (ESI-TOF) m/z ($C_{12}H_{12}O_3$): Calculated 205.0865 ($M+H^+$) / Found 205.0854 ($M+H^+$).

2-(2-chlorophenyl)cyclopentane-1,3-dione.

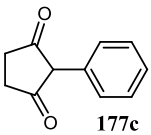


185c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 6:1). Product **185c** was obtained in a 30% isolated yield as a yellow oil.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.42 (m, 2H), 7.32 (m, 2H), 3.97 (s, 1H), 2.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 207.03, 203.43, 133.36, 130.16, 129.65, 129.53, 128.88, 126.90, 65.53, 31.47, 22.54. HRMS (ESI-TOF) m/z ($C_{11}H_9ClO_2$): Calculated 209.0369 ($M+H^+$) / Found 209.0362 ($M+H^+$).

2-phenyl-cyclopentane-1,3-dione.

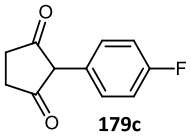


177c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 4:1). Product **177c** was obtained in a 20% isolated yield as a yellow oil. Substrate was already reported in *Synth. Commun*. **1989**, *19*, 2741.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.46 (m, 2H), 7.37 (m, 3H), 3.99 (s, 1H), 2.57 (m, 1H), 2.36 (m, 2H), 2.17 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.45, 129.98, 128.48, 128.30, 127.17, 67.61, 32.20, 22.20. HRMS (ESI-TOF) m/z ($C_{11}H_{10}O_2$): Calculated 197.0578 ($M+Na^+$) / Found 197.0564 ($M+Na^+$)

2-(4-fluorophenyl)cyclopentane-1,3-dione.

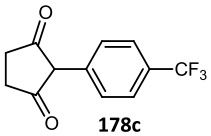


179c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **179c** was obtained in a 17% isolated yield as a yellow oil. Substrate was already reported in K. M. Gottesdiener, S. A. Green, E. Macintyre, **2007**, WO 2007/146224 A2.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.43 (d, J = 8Hz, 1H), 6.77 (d, J = 8Hz, 1H), 3.98 (s, 1H), 2.57 (m, 1H), 2.35 (m, 2H), 2.16 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 216.68, 128.98, 115.34, 67.52, 29.56, 21.93. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ = -112.93 HRMS (ESI-TOF) m/z ($C_{11}H_9FO_2$): Calculated 193.0665 ($M+H^+$) / Found 193.0657 ($M+H^+$).

2-(4-trifluoroethylphenyl)cyclopentane-1,3-dione.

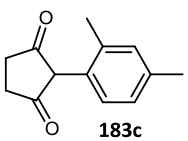


178c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **178c** was obtained 21% I.Y. as a yellow solid.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.51 (d, J = 8Hz, 1H), 6.90 (d, J = 8Hz, 1H), 4.00 (s, 1H), 2.60 (m, 1H), 2.40 (m, 2H), 2.19 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.24 ppm, 127.69, 125.45, 115.51, 68.19, 32.07, 22.21. ^{19}F NMR ($CDCl_3$, 376.8 MHz): δ = -62.75 ppm (s). HRMS (ESI-TOF) m/z ($C_{12}H_9F_3O_2$): Calculated 243.0633 ($M+H^+$) / Found 243.0627 ($M+H^+$).

2-(2,4-dimethylphenyl)cyclopentane-1,3-dione.

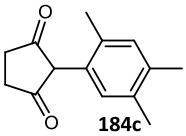


183c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **183c** was obtained in a 28% I.Y. as a colorless oil. Substrate was already reported in Th. N. Wheeler, **1982**, US 4338122 A.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.19 (d, J = 8Hz, 1H), 7.03 (s, 1H), 7.01 (d, J = 8Hz, 1H), 3.97 (s, 1H), 2.50 (m, 2H), 2.32 (s, 3H), 2.26 (m, 2H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.76, 138.81, 136.95, 131.55, 130.68, 128.18, 126.33, 64.92, 31.50, 22.59, 21.19, 19.52. HRMS (ESI-TOF) m/z ($C_{13}H_{14}O_2$): Calculated 225.0891 ($M+Na^+$) / 225.0889 ($M+Na^+$).

2-(2,4,5-trimethylphenyl)cyclopentane-1,3-dione.

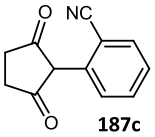


184c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **184c** was obtained in a 16% I.Y. as a yellow oil.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.87 (s, 1H), 6.58 (s, 1H), 3.97 (s, 1H), 2.51 (m, 2H), 2.30 (m, 2H), 2.22 (s, 3H), 2.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 209.07, 137.41, 133.96, 132.55, 131.21, 129.41, 128.40, 64.74, 31.16, 22.52, 19.66, 19.17, 18.65. HRMS (ESI-TOF) m/z ($C_{14}H_{16}O_2$) = Calculated 217.1229 ($M+H^+$) / Found 217.1230 ($M+H^+$).

2-(2-cyanophenyl)cyclopentane-1,3-dione:

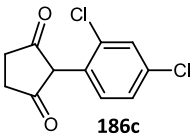


187c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **187c** was obtained in a 14% I.Y. as a yellow oil.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.84 - 7.49 (m, 4H), 4.11 (s, 1H), 2.47 (m, 4H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.08 ppm, 133.59, 132.94, 132.88, 132.27, 130.57, 129.21, 128.94, 65.74, 31.26, 22.32. HRMS (ESI-TOF) m/z ($C_{12}H_9NO_2$): Calculated 200.0712 ($M+H^+$) / Found 200.0703 ($M+H^+$).

2-(2,4-dichlorophenyl)cyclopentane-1,3-dione.

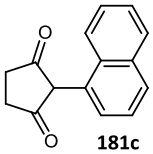


186c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **186c** was obtained in a 20% I.Y. as a white solid. Subtrate was already characterized by Th. N. Wheeler, **1982**, US 4338122 A.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.41 (s, 1H), 7.36 (d, J = 8Hz, 1H), 7.30 (d, J = 8Hz, 1H), 3.96 (s, 1H), 2.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 206.39, 135.37, 130.44, 128.51, 128.14, 127.46, 65.38, 31.17, 22.30. HRMS (ESI-TOF) m/z ($C_{11}H_8Cl_2O_2$): Calculated 260.0245 ($M+NH_4^+$) / Found 260.0247 ($M+NH_4^+$).

2-(naphthalen-1-yl)cyclopentane-1,3-dione:



181c

This product was purified by flash chromatography silica gel (petroleum ether / EtOAc : 8:1). Product **181c** was obtained in a 28% I.Y. as a colorless oil.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.89 (d, J = 8Hz, 1H), 7.64 - 7.51 (m, 6H), 4.13 (s, 1H), 2.62 (m, 2H), 2.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 208.61, 133.33, 131.60, 129.57, 128.76, 126.96, 126.70, 126.61, 126.04, 125.14, 124.11, 65.13, 31.73, 22.65. HRMS (ESI-TOF) m/z ($C_{15}H_{12}O_2$): Calculated 247.0735 ($M+Na^+$) / Found 247.0737 ($M+Na^+$).

6.5. References

[1] I. –H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki*, J. Am. Chem. Soc.* **2009**, *131*, 11664.

[2] G. Palau-Lluch, E. Fernández, *Adv. Synth. Catal.* **2013**, *355*, 1464.

[3] J. Liu, J. Chan, C. M. Bryant, P. A. Duspara, E. E. Lee, D. Powell, H. Yang, Z. Liu, Ch. Walpole, E. Roberts, R. A. Batey, *Tetrahedron Letters* **2012**, *53*, 2971.

[4] G. Palau-Lluch, X. Sanz, E. La Cascia, M. G. Civit, N. Miralles, A. B. Cuenca, E. Fernández. *Pure and Applied Chemistry*, **2015**, *87*, 181.

[5] N. Ngatimin, Ch. J. Gartshore, J. P. Kindler, S. Naidu, D. W. Lupton, *Tetrahedron Letters* **2009**, *50*, 6008.

[6] F. Nahra, Y. Macé, D. Lambin, O. Riant, *Angew. Chem. Int. Ed.* ***2013****, 52, 3208.*

[7] F. –X. Felpin *J. Org. Chem,* **2005**, *70*, 8575.

[8] K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J*, **2014**, *20*, 12032.

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

[10] a) G. Tojo, M. Fernández (**2006**), *Oxidation of alcohols to aldehydes and ketones. A guide to current common practice.* Santiago de compostela, Spain. Springer; b) J. Carr, T.S. Snowden, *Tetrahedron.,* **2008**, *64*, 2897.

[11] G. Palau-Lluch, E. Fernández, *Cat. Sci. and Tech.* (Submitted).

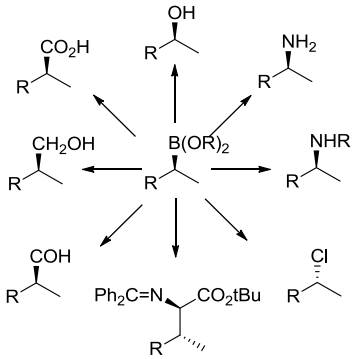
7. Summary

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

Organoboranes are of great interest in both synthetic and organic chemistry and biomedical sciences[1]. The main advantages of using organoboranes as intermediates in organic synthesis is their versatile reactivity, stability and easy accessibility[1]. In particular, the catalytic C-B bond formation can be considered as an ideal mean to introduce functionalities and obtain target products with high control of chemo-regio-and stereoselectivity (Scheme 7.1).



Scheme 7.1. *Specific transformations of the C-B bond.*

As part of the work to prepare novel organoboron compounds, chemists developed a process which is commonly known as β-boration (or boron conjugate addition, BCA)[2]. This is a process by which diboron species [e.g. B_2pin_2 (pin = $OCMe_2CMe_2O$) **1**, B_2cat_2 (cat = 1,2-$O_2C_6H_4$) **2**, B_2neop_2 (neop = $OCH_2CMe_2CH_2O$) **3**, B_2hex_2 (hex = $OC(Me)_2CH_2CH(Me)O$) **4** (Figure 7.1) undergo Michael-type conjugate addition to an electron-deficient alkene **5**, leading to a 1,4-addition adduct **6** (boron enolate) which after work-up, yields the β-boration product (Figure 8.1).

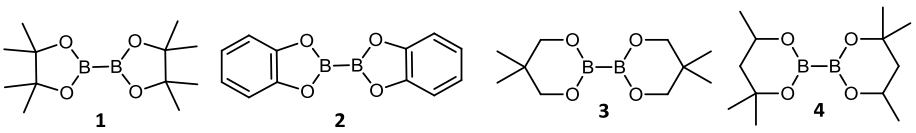


Figure 7.1. *Diboron species B_2pin_2 **1**, B_2cat_2 **2**, B_2neop_2 **3** and $B_2(hex)_2$ **4**.*

The aim of this thesis is that despite the great amount of work performed in the field of boron conjugate addition, there are still several limitations and not general procedures for the obtantion of highly functionalized products starting from simple α,β-unsaturated substrates. Therefore, what we want to do is develop and obtain different methodologies for the synthesis of α-functionalized β-borylated carbonyl compounds.

In this context, fluorine atoms, specially whilst bonded to carbon bonds taking part as fluoroalkyl substituents, are of a considerable importance considering the physicochemical properties that those C-F bonds have to offer to the molecule itself.

α-fluorination of carbonyls, α'-ketocarbonyls, and related carbonyl derivatives has been achieved also by using electrophilic fluorinating reagents such as NFSI (**49**) and F-TEDA-BF_4 (**50**). Chiral versions of this transformations can also be achieved when chiral ligands are used (Figure 7.2).

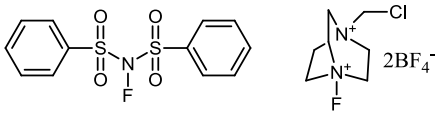
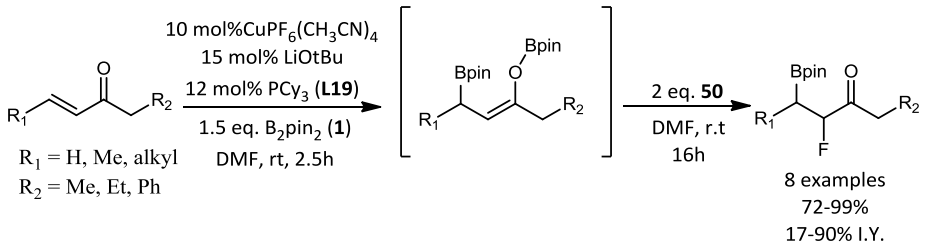


Figure 7.2. *Molecular structure of electrophilic fluorinating reagents.*

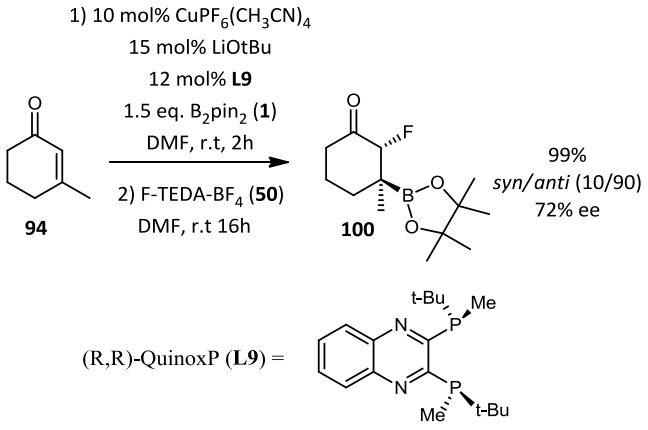
For the electrophilic fluorinating reagents to interact with the carbonyl, the carbonyl needs to be transformed into the corresponding nucleophile (enol, enolate or enamine), thus, as a matter of compatibility with the borylation reaction, we envisaged a system where the enol formed upon boron conjugate addition to the electron deficient unsaturated substrate, instead of being protonated using MeOH as the additive, it could be further reacted with another electrophile, being in this case an electrophilic fluorinating reagent.

For the optimized results obtained, we took conditions from the MeOH free borylation protocol reported by Shibasaki et al.[3] and we modified them slightly to favor the addition of electrophilic fluorinating reagent. The in-situ formed 1,4-diborated compound reacted with the electrophilic source obtaining a considerable substrate scope of α-fluorinated β-borylated carbonyl compounds (Scheme 7.2). *Trans* and *cis* diaestereoselection was substrate dependant, even though the *trans* diaestereisomer was always the favored.



Scheme 7.2. *Scope of α-fluoro β-boryl ketones from α,β-unsaturated ketones.*

Also, substrate 3-methyl 2-cyclohexen-1-one was borylated with $CuPF_6(CH_3CN)_4$ and QuinoxP*, and further addition of the electrophilic fluorine source, led to the corresponding α-fluorinated β-borylated cyclic enone in similar values of conversion and *cis/trans* diaestereoselection, and this time as well, up to 72 % ee (Scheme 7.3). This synthetic approach represents an alternative to the current efforts to develop enantioselective aliphatic fluorination routes.



Scheme 7.3. *Enantioselective one-pot borylation/fluorination sequence.*

At that point of the research, in which we have explored a metal catalyzed methodology in order to obtain our desired compounds, we also wanted to test if in a metal free context, the fluorination/borylation of ketones can be possible.

We turned our attention to an alternative fluorination protocol via in situ formation of a nucleophilic enol intermediate under acidic conditions. The efficiency of this direct electrophilic fluorination of ketones has recently been demonstrated by Batey et al.[9]. The reactions are generally quite selective leading to the formation of monofluorinated products.

Since this reaction has been reported to proceed most efficiently in MeOH, we found a principle of compatibility with the organocatalytic β-boration carried out in MeOH as solvent.

Therefore, we performed an organocatalytic β-boration of α,β-unsaturated ketones followed by the addition of 2 eq. of F-TEDA-BF_4 (**50**) and 10 mol% of H_2SO_4. Upon optimized conditions, a scope of substrates have been successfully borylated and then electrophilically fluorinated using F-TEDA-BF_4 (**50**) and catalytic amounts of H_2SO_4 conc. Interestingly, not only B_2pin_2 (**1**) was a compatible reagent for borylation, also B_2hex_2 (**3**) and B_2neop_2 (**4**) could be used as borylation reagents (Scheme 7.4). The products obtained offered 1/1 diaestereselection *trans*/*syn*.

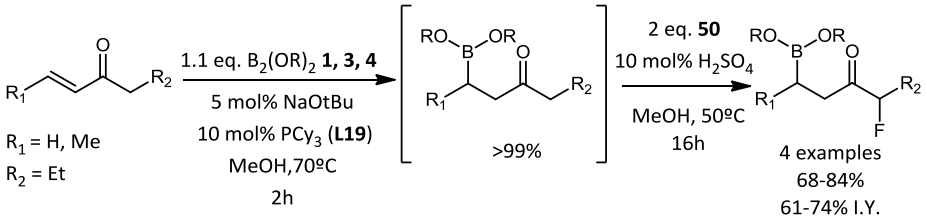
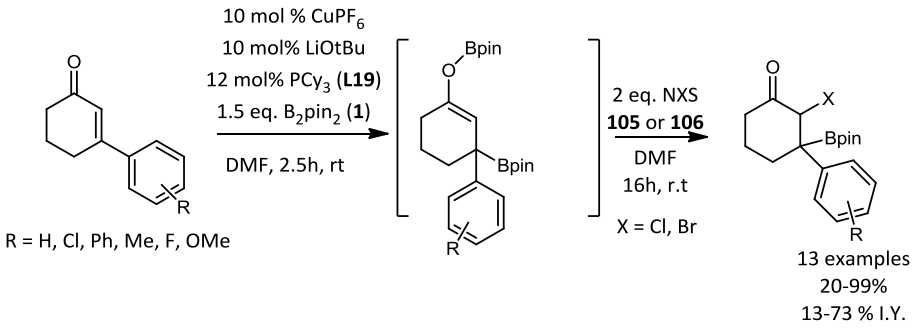


Table 7.4. *Scope of α'-fluoro β-boryl ketones from α,β-unsaturated ketones.*

Next, we focused on the difunctionalization of α,β-unsaturated carbonyl compounds using halogenating reagents to obtain α-chloro and α-bromo β-boryl compounds, respectively. We first envisaged that using the most typically worn electrophilic halogenating reagents NCS (**105**) and NBS (**106**), we could obtain similar results in terms of conversion and regioselection as those we previously obtained using electrophilic fluorinating reagent F-TEDA-BF_4 (**50**)[5]. That was however not the case, until we applied a similar methodology to β-substituted α,β-unsaturated cyclohexenones, where we obtained moderate to good values of conversion and isolated yields using both NCS and NBS as chlorinating and brominating reagents.



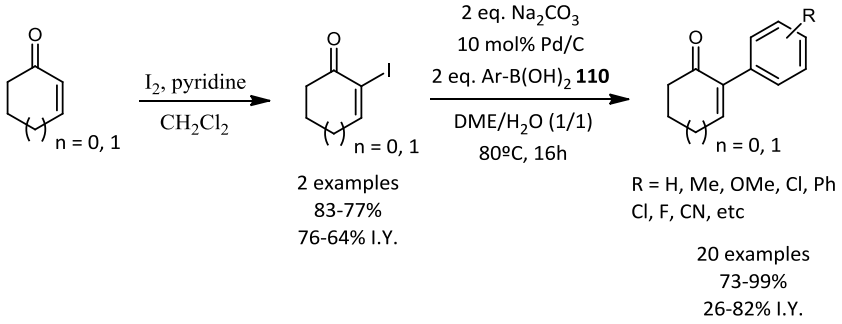
Scheme 7.5. *Cu-catalyzed borylation/halogenation of β-substituted cyclic enones.*

To extend the substrate scope, we applied an existing methodology for the synthesis of α-chloroenones[6] that we envisaged we could borylate using a boron conjugate addition

methodology. Nevertheless, from the ten α-chloroenones synthesized, only two could be successfully borylated to obtain the corresponding α-halo β-boryl ketone.

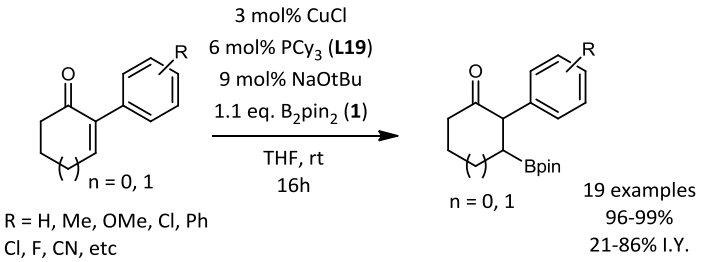
Finally, still in the field of difunctionalization, we envisaged the formation of α-aryl-β-boryl cyclic ketones as potential intermediates for the synthesis of 2-aryl-1,3-diones, which are compounds suitable as pesticides.

We applied first a step wise methodology in which we synthesized α-iodoenones, and then we submitted them to Pd/C catalyzed cross-coupling with arylboronic acids using an already reported methodology[7], obtaining a vast substrate scope of α-arylated cycloenones in good to excellent yields (Scheme 7.6).



Scheme 7.6. *Step wise iodination and arylation of cyclic enones.*

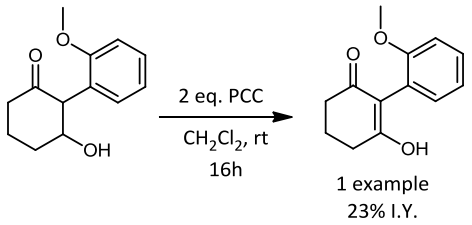
Further borylation conditions using catalytic amounts of CuCl in THF led us towards to obtantion of the corresponding borylated compounds, being the first time that α-aryl β-boryl ketones are reported in the literature. Mostly all the products obtained displayed trans-diaestereoselection (Scheme 7.7).



Scheme 7.7. *Cu-catalyzed borylation of α-aryl cyclic enones.*

As the last step, we envisaged an oxidation protocol using $NaOH/H_2O_2$ system to obtain the corresponding alcohol, that then we would oxidize to the C=O group to obtain the final 1,3-

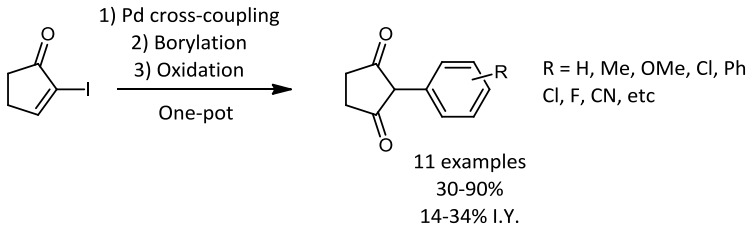
dione. In the case of the cyclohexanones, the last oxidation step was more complicated, due that elimination was always favored, and only one substrate could be fully transformed to the corresponding dione, step wise, using PCC as the oxidant[8] (Scheme 7.8).



Scheme 7.8. *PCC mediated oxidation of 2-aryl-3-hydroxy cyclic enone.*

When we applied the same C-B → C-OH oxidation methodology for the corresponding 5-membered ring α-aryl β-boryl cycloenones, we were delighted to observe that we obtained in high conversions the corresponding 2-aryl-1,3-diones in one single step.

Encouraged by the results obtained for the cyclopentenones, we performed the one-pot protocol for the synthesis of 2-aryl-1,3-diones from α-iodoenones, and we were able to obtain up to 11 different diones, being some of them for the first time reported in the literature.



Scheme 7.9. *One-pot synthesis of 2-aryl-1,3-diones from α-iodocyclopentenone.*

[1] a) E. L. Muetterties, *The Chemistry of Boron and Its Compounds* (John Wiley & Sons Inc., New York, **1967**); b) D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**, 48; c) G. Hall, *Boronic Acids*; Wiley-VCH: Weinheim, Germany, **2005**.

[2] J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.* **2012**, *41*, 3558.

[3] I. –H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki*, J. Am. Chem. Soc.* **2009**, *131*, 11664.

[4] J. Liu, J. Chan, C. M. Bryant, P. A. Duspara, E. E. Lee, D. Powell, H. Yang, Z. Liu, Ch. Walpole, E. Roberts, R. A. Batey, *Tetrahedron Letters* **2012**, *53*, 2971.

[5] G. Palau-Lluch, E. Fernández, *Adv. Synth. Catal.* **2013**, *355*, 1464.

[6] N. Ngatimin, Ch. J. Gartshore, J. P. Kindler, S. Naidu, D. W. Lupton, *Tetrahedron Letters* **2009**, *50*, 6008.

[7] F. –X. Felpin *J. Org. Chem,* **2005**, *70*, 8575.

[8] a) G. Tojo, M. Fernández (**2006**), *Oxidation of alcohols to aldehydes and ketones. A guide to current common practice.* Santiago de compostela, Spain. Springer; b) J. Carr, T.S. Snowden, *Tetrahedron.,* **2008**, *64*, 2897.

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

8. Appendix

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

Publications

Type of publication: Journal

Status: Published

Date: May 2013

Name of publication: Building functionality through sequential C-B and C-F bond formation.

Publisher and full reference: Advanced Synthesis and Catalysis, **2013**, *355*, 1464-1470.

Authors: G. Palau-Lluch, Elena Fernández.

Type of publication: Journal

Status: Published

Date: February 2015

Name of publication: Organocatalytic functionalization through boron chemistry.

Publisher and full reference: *Pure and Applied Chemistry*, **2015**, *87*, 181-193.

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

Type of publication: Journal

Status: Submitted

Date: April 2015

Name of publication: Synthesis of 2-aryl-1,3-diones through borylation chemistry.

Publisher and full reference: *Catalysis Science and Technology*

Authors: G. Palau-Lluch, E. Fernández.

Congress contributions

September 2014:

Autors: G. Palau-Lluch, E. Fernández.

Title: Sequential β-boration/α-chlorination of α,β-unsaturated carbonyl compounds.

Participation as: Poster.

Conference: GEQO XXXII meeting (Expert Group on Organometallic Chemistry)

Place: Tarragona (Spain).

Active participation on the organization and development of the conference.

August 2014:

Autors: G. Palau-Lluch, E. Fernández.

Title: Sequential β-boration/α-chlorination of α,β-unsaturated carbonyl compounds.

Participation as: Poster.

Conference: IME BORON XV.

Place: Prague (Czech Republic).

September 2013:

Autors: G. Palau-Lluch, E. Fernández.

Title: Building functionality through sequential C-B and C-F bond formation.

Participation as: Flash presentation and poster.

Conference: European Conferences on Boron Chemistry (Euroboron6).

Place: Radziejowice (Poland).

May 2013:

Autors: G. Palau-Lluch, E. Fernández.

Title: Building functionality through sequential C-B and C-F bond formation.

Participation as: Poster.

Conference: 96th Canadian Chemistry Conference and Exhibition.

Place: Quebec (Canada).

July 2012:

Autors: G. Palau-Lluch, E. Fernández.

Title: Catalytic borylation/fluorination of α,β-unsaturated carbonyl compounds. A new approach towards polifunctionalization.

Participation as: Poster.

Conference: 18th International Symposium on Homogeneous Catalysis.

Place: Toulouse (France).

July 2012:

Autors: G. Palau-Lluch, E. Fernández.

Title: Catalytic borylation/fluorination of α,β-unsaturated carbonyl compounds. A new approach towards polifunctionalization.

Participation as: Poster.

Conference: CEICS Nobel Campus.

Place: Tarragona (Spain).

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015

α,β-DIFUNCTIONALIZATION OF α,β-UNSATURATED CARBONYL COMPOUNDS THROUGH BORYLATION REACTION.
Gerard Palau Lluch
Dipòsit Legal: T 1358-2015