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# Synthesis of iodo-diborylmethylsilane and reactivity with cyclohexanone

BACHELOR'S THESIS

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Dept. Química Física i Inorgànica

Bachelor's Degree in Chemistry

UNIVERSITAT ROVIRA i VIRGILI

Tarragona

2023

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## ACKNOWLEDGEMENTS

This research work would not have been possible without the help and guidance of my supervisor, Prof. Elena Fernández, to whom I would like to express my utmost gratitude. I am very grateful to have been given this opportunity to experience the world of research in first person. Thank you for all the advice and support given throughout all this time, and especially, thank you for transmitting the passion you have about boron chemistry every day.

On the other hand, I would like to thank all the members of the research group CatBorChem, who have made every day better, creating a great and friendly atmosphere in the laboratory and in the seminar of inorganic chemistry of the faculty. Especially, I would like to thank Dr. Oriol Salvadó, who not only has he been my supervisor in the laboratory but also a good friend. Thank you for sharing with me all your knowledge inside and outside the laboratory, for your patience and for all your advices. You have really made this an unforgettable experience and every day of work worth it. I would also like to thank my colleague Alba Mesas, with whom I have had the pleasure of sharing this time with as well. Thank you for being so kind to me, for all the jokes and laughs in the laboratory, and especially for giving me support during the most difficult times, this journey would not have been the same without you two.

I would also like to thank the friends I have made along these last four years, thank you Laura Solé, Mario Villares, Marta López and Nerea Iragorri, it is because of you that I have so many good memories from these years, you have made even the worst days incredible. We have laughed, cried and suffered, but everything has been all together, which makes the bad moments not so bad, and the good moments even better. I am incredibly grateful to have had the opportunity to meet you, and even though this journey comes to an end, the memories of all these years will live on forever, thank you.

Finally, this would not be a proper acknowledgement without mentioning my family. Thank you for always being there, I will be forever grateful for all the help that you have given me.

# 1. ABSTRACT

**English:**

The present work is aimed to get an experience in the world of research, more specifically, in the field of organoboron chemistry, and everything it involves: bibliographic research, design of experiments, development of organoboron reactions, purification of reaction crudes, characterization of the products and interpretation of the results.

Within this work, a novel *gem*-diborylalkane has been synthesized, and its reactivity in front of cyclohexanone has been studied in the presence of several lithiated bases. The formation of a novel product has been observed, and together with the different experiments carried out, a plausible mechanistic route has been proposed for this new kind of reactivity.

This works opens the possibility to study a new type of reactivity of *gem*-diborylalkanes.

**Català:**

Aquest treball de fi de grau està enfocat en adquirir experiència en el món de la recerca, concretamente, en el camp de la química organoborada i tot allò que implica: recerca de literatura, disseny d'experiments, desenvolupament de reaccions organoborades, purificació de crus de reacción, caracterització dels productes i la interpretació dels resultats.

En aquest context, s'ha sintetitzat un nou *gem*-diborilalcà i s'ha estudiat la seva reactivitat davant de la ciclohexanona en presència de diverses bases litiades, on s'ha observat la formación d'un nou producte, i juntament amb els resultats dels diferents experiments que s'han dut a terme, s'ha proposat una possible ruta mecanística per aquest nou tipus de reactivitat.

Aquest treball obre la possibilitat de l'estudi d'un nou tipus de reactivitat dins de la familia dels *gem*-diborilalcans.

The present Bachelor's thesis has been developed at the Inorganic Chemistry Area in Dept. Química Física i Inorgànica of the University Rovira i Virgili, in the research group of Catalytic Organoboron Chemistry, CatBorChem.
(http://www.quimica.urv.es/organoborane/index.php).

## 2. INTRODUCTION

Organoboron compounds are useful building blocks in the field of organic synthesis due to their good functional group tolerance and their low toxicity. Over the last decades, organoboron chemistry has provided synthetic chemists with powerful tools for the construction of complex organic molecules with precise control over stereochemistry and functional group compatibility.[1] For that reason, the development of organoboron chemistry has greatly expanded the synthetic toolbox, particularly by breakthroughs in the chemistry of *gem*-diborylalkanes, as they enable C-C bond formation through deborylation or deprotonation sequences.[2–4] Such compounds have become very important intermediates in organic synthesis and in organometallic chemistry, and structurally, they consist of two boryl groups bonded to a single carbon atom (Figure 1).

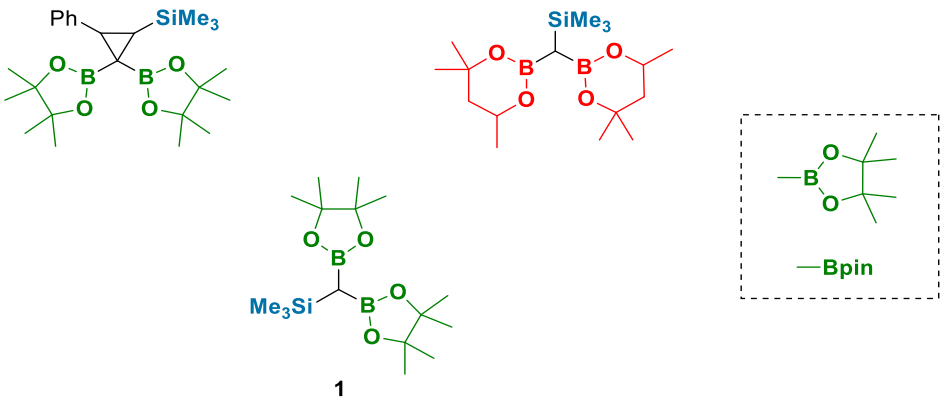
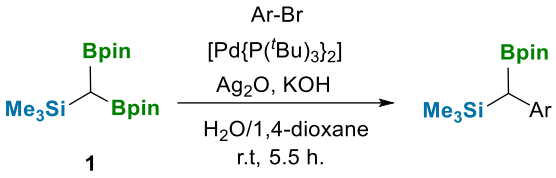



**Figure 1.** Representative examples of *gem*-diborylalkanes.

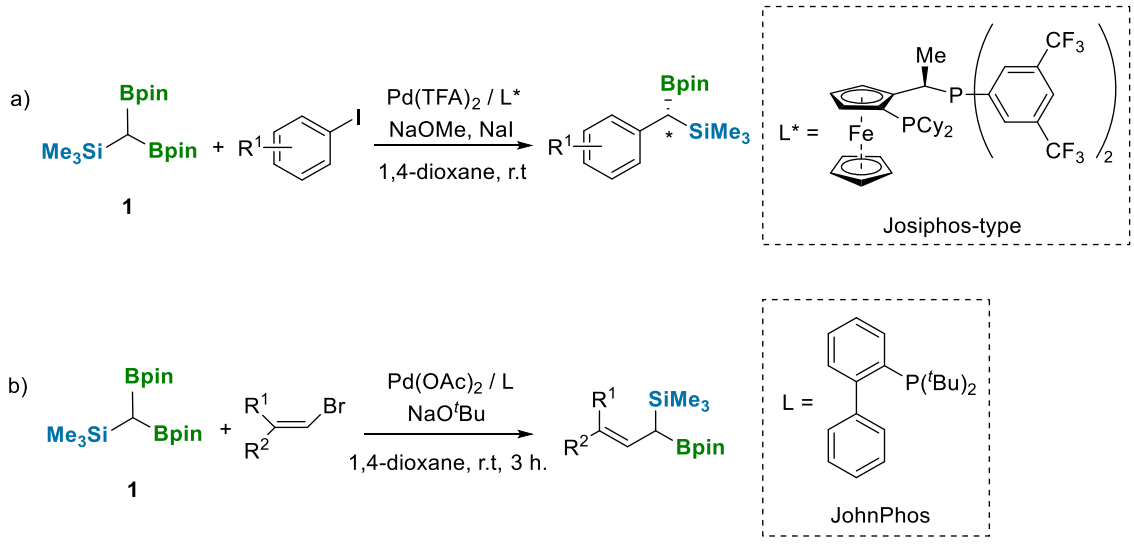
One of the most important compounds within the family of *gem*-diborylalkanes is (bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane (**1**), which was synthesized for the first time by Endo and co-workers in 2013,[5] with the aim of obtaining benzyl-boronate derivatives bearing a trimethylsilyl group at the benzylic position. The authors showed that the chemoselective Suzuki-Miyaura cross-coupling reaction of diborylmethylsilane and aryl halides proceeded at room temperature when silver oxide

and KOH were added (Scheme 1), increasing the efficiency of the reaction with yields up to 98% on the benzyl-boronate derivative.[5]



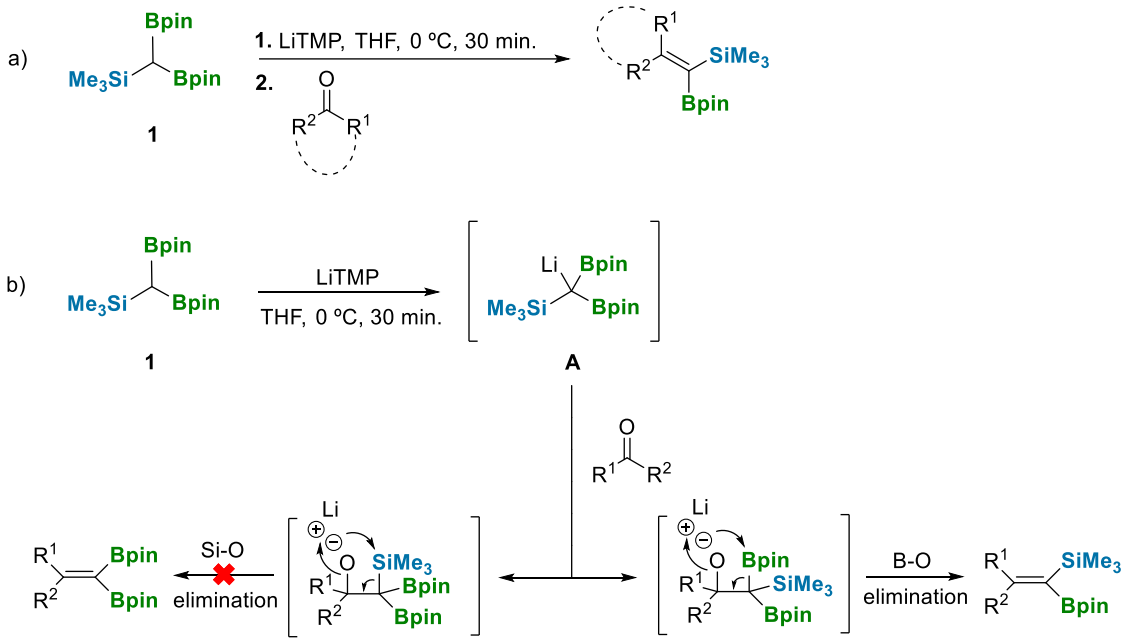

**Scheme 1.** Pd catalyzed C-C formation with diborylmethylsilane **1**.

More recently, in 2018, Cho and co-workers further enriched the chemistry of diborylmethylsilane **1** by developing a method to synthesize chiral benzylic 1,1-silylboronate esters, consisting of a Suzuki-Miyaura cross-coupling reaction of diborylmethylsilane **1** with aryl iodides (Scheme 2a). They identified $Pd(TFA)_2$ (TFA = Trifluoroacetate) as the source of palladium catalyst, and a Josiphos-type diphosphine, bearing a 3,5-bis(trifluoromethyl)phenyl moiety, as the ligand for the palladium catalyst. The presence of NaOMe, as a base, and NaI, as an additive, promoted the reaction up to 90% yield with excellent enantioselectivity.[6] Later on, Cho and co-workers developed another palladium-catalyzed chemoselective cross-coupling reaction between diborylmethylsilane **1** and alkenyl bromides to access α-silyl-substituted allylic boronate esters. The authors demonstrated that the use of NaO$^t$Bu as a base and JohnPhos as a ligand for the catalyst, $Pd(TFA)_2$, improved the efficiency of the catalytic process significantly with yields up to 74% (Scheme 2b).[7]




**Scheme 2**. a) Pd-catalyzed enantioselective cross-coupling of diborylmethylsilane **1** with aryl iodides. b) Pd-catalyzed chemoselective cross-coupling of diborylmethylsilane **1** with alkenyl bromides.

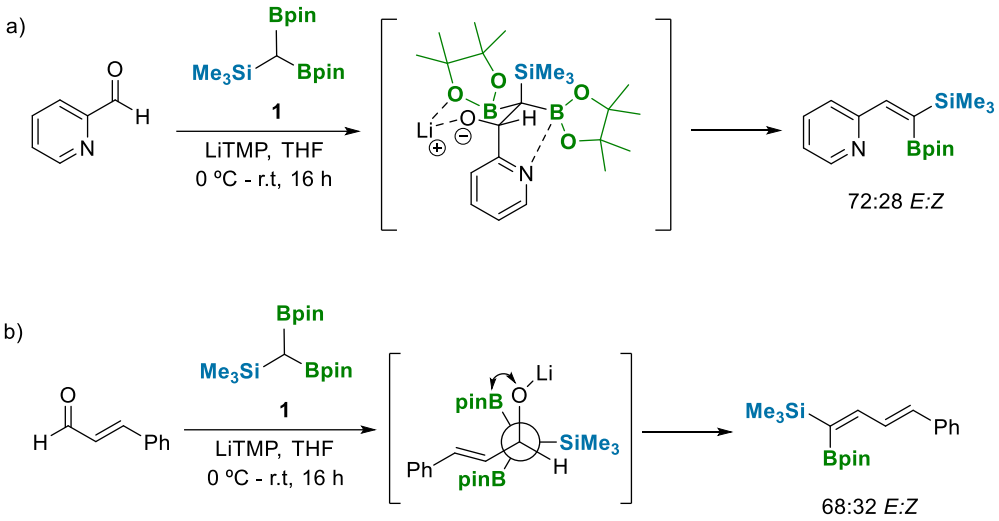
Complementing the application of compound **1** in Suzuki-Miyaura cross-coupling reactions, Fernández and co-workers[8] developed, in 2016, an opportune *gem*-silylborylation of symmetric and non-symmetric ketones, using diborylmethylsilane **1** as a novel olefination agent. Furthermore, the reactivity of such compounds has been explored thoroughly, enabling the formation of tetrasubstituted 1,1-silylborylalkenes in a stereoselective way (Scheme 3a). The reaction takes place in two consecutive steps, where the first one proceeds through the deprotonation of diborylmethylsilane **1** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and the subsequent formation of a lithium diborylsilylmethide salt **A** (Scheme 3b). The ketone is added afterwards into the solution, and at that point, the reaction could proceed through either a Petterson-type Si-O elimination to afford a *gem*-diborylalkene or through the boron-Wittig-type B-O elimination to access *gem*-silylborylalkenes. Fernández and co-workers observed that the process was chemoselective towards the B-O elimination due to the oxophilicity of the boron atom (Scheme 3b).[8]




**Scheme 3**. a) Boron-Wittig olefination between ketones and diborylmethylsilane **1**. b) Selective B-O elimination (right) *versus* Si-O elimination (left).

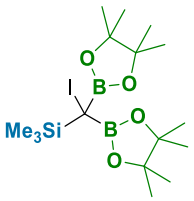
The reactivity of diborylmethylsilane **1** in front of aliphatic and aromatic aldehydes was also explored by Fernández and co-workers.[9] They illustrated that the trimethylsilyl group of diborylmethylsilane **1** determined the regioselectivity of the reaction due to its size, favoring the formation of the *(E)*-borylsilylalkene. On the other hand, the boron atoms of diborylmethylsilane **1** played a key role in the regioselectivity of the reaction when heterocyclic aromatic aldehydes were used, involving stereodetermining intermediates *via* an interaction between the heteroatom of the aromatic ring of the aldehyde and one

of the boron atoms of diborylmethylsilane **1**, favoring the formation of the *(E)*-borylsilylalkene (Scheme 4a). Moreover, the authors showed that the use of α,β-unsaturated aliphatic aldehydes allowed to access 1,1-silylborylated conjugated dienes and diynes with high regioselectivity due to the higher stability of the intermediate where the trimethylsilyl group of diborylmethylsilane **1** is eclipsing the hydrogen atom of the aldehyde (Scheme 4b).[9]




**Scheme 4.** a) Stereodetermining interactions in the boron-Wittig reaction between an heterocyclic aromatic aldehyde and diborylmethylsilane **1**. b) Stereodetermining eclipsed conformation of intermediates in the boron-Wittig reaction between α,β-unsaturated aliphatic aldehydes and diborylmethylsilane **1**.

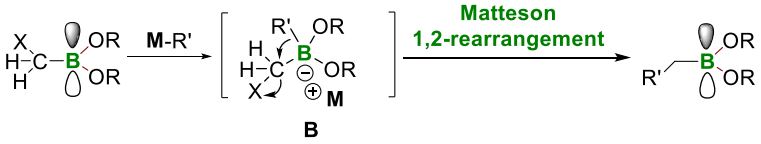
Within this context, the novel reagent iodo-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane (**2**) (Figure 2), is planned to be synthesized through iodination reactions of diborylmethylsilane **1** using several iodinating agents such as $I_2$ or *N*-iodosuccinimide. Due to the structural similarities between diborylmethylsilane **1** and iodo-diborylmethylsilane **2**, it is interesting to assess the reactivity of this new compound in front of cyclic symmetric ketones, such as cyclohexanone, aimed to compare the reactivity with that of diborylmethylsilane **1**.




**2**

**Figure 2.** Structure of iodo-diborylmethylsilane **2**.

The combination of the halide and boryl moiety within the same structure makes iodo-diborylmethylsilane **2** an ideal reagent to undergo 1,2-migration protocols, originally observed by Matteson and co-workers in alkylboronic esters (Scheme 5).[10]




**Scheme 5**. Mechanism of a Matteson 1,2-rearrangement.

The sequence begins with the attack of a nucleophile to the boryl group in the alkylboronic ester, forming a boron "ate" complex **B** that quickly undergoes a 1,2-rearrangement, displacing any suitable leaving group from the α-carbon, thus forming a new sigma bond between the α-carbon and the nucleophile.

That kind of migrations cannot take place in diborylmethylsilane **1** due to the lack of a good leaving group in the α-carbon, hence, reactions between compound **1** and ketones follow the boron-Wittig mechanism. On the other hand, Matteson rearrangements can take place in iodo-diborylmethylsilane **2**, opening up the possibility of the formation of new products. For this reason, the study of this kind of reactivity between $IC(Bpin)_2(SiMe_3)$ (**2**) and ketones remains as one of the main objectives of this present work.

## 3. OBJECTIVES

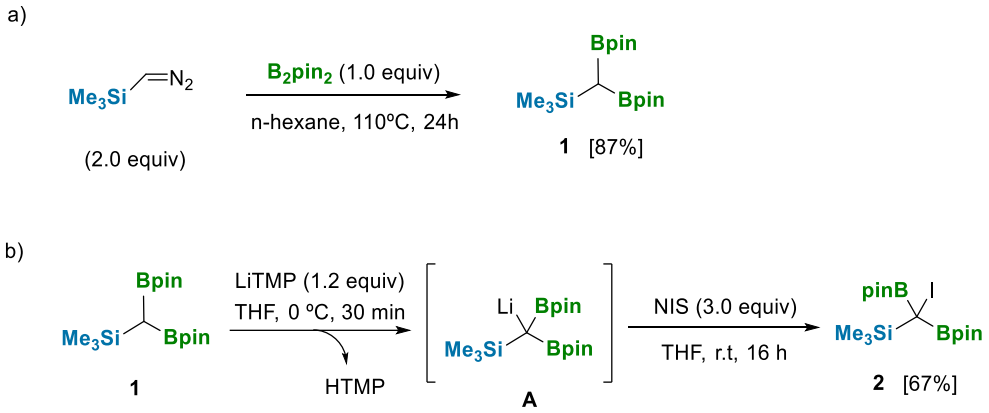
The focus of this research work is the development of an efficient synthesis of the new reagent iodo-diborylmethylsilane **2**, to establish the compatibility between the bulkiness and electron donating properties of the trimethylsilyl group, and the electron-withdrawing properties of iodide, both in the formation of iodo-diborylmethylsilane **2** as well as in the homologative coupling with ketones.

Towards this end, the following objectives have been planned:

1. To synthesize the new *gem*-diborylsilylalkane compound $IC(Bpin)_2(SiMe_3)$ (**2**) from the reagents $HC(Bpin)_2(SiMe_3)$ (**1**) and *N*-iodosuccinimide (NIS), in the presence of a base.
2. To characterize the new compound iodo-diborylmethylsilane **2**.
3. To study the behavior of compound $IC(Bpin)_2(SiMe_3)$ (**2**) in front of several lithiated bases, and assess its reactivity with cyclohexanone.
4. To characterize the product of the homologative coupling between iodo-diborylmethylsilane and cyclohexanone, identified as trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-oxaspiro[2.5]octan-2-yl)silane (**6**).

The first goal in this project was the synthesis of the new halo-diborylmethylsilane derivative, iodo-diborylmethylsilane **2**, from the reagent $HC(Bpin)_2(SiMe_3)$ (**1**). Towards this end, compound **1** was first synthesized following the general procedure described previously in the research group,[8] which was isolated in 87% yield, as described in the experimental part of this manuscript (Scheme 6a).

The characterization of product **1** was conducted through NMR spectroscopy, and the data obtained was in agreement with that of the reported product.[8]




**Scheme 6.** a) Synthesis of $HC(Bpin)_2(SiMe_3)$ (**1**) from bis(pinacolato)diboron ($B_2pin_2$) and (trimethylsilyl)diazomethane. b) Synthesis of iodo-diborylmethylsilane **2** *via* deprotonation and iodination of diborylmethylsilane **1**.

After compound **1** was prepared, the synthesis of iodo-diborylmethylsilane **2** was carried out for the first time in this work, following the general procedure described in the experimental part of this manuscript. The addition of 1.2 equivalents of LiTMP to diborylmethylsilane **1** triggers the *in situ* formation of the lithium diborylsilylmethide salt **A** *via* an acid-base reaction. Intermediate **A** reacts with the iodinating agent, *N*-iodosuccinimide (NIS) to afford the final product **2** in 67% isolated yield (Scheme 6b).

The characterization of the novel diborylmethylsilane derivative, $IC(Bpin)_2(SiMe_3)$ (**2**) was conducted through NMR spectroscopy. The $^1H$ NMR data for compound **2** can be compared with the $^1H$ NMR data of the analogue compound $ICH(Bpin)_2$, that has been described recently in the literature (Figure 3).[11]

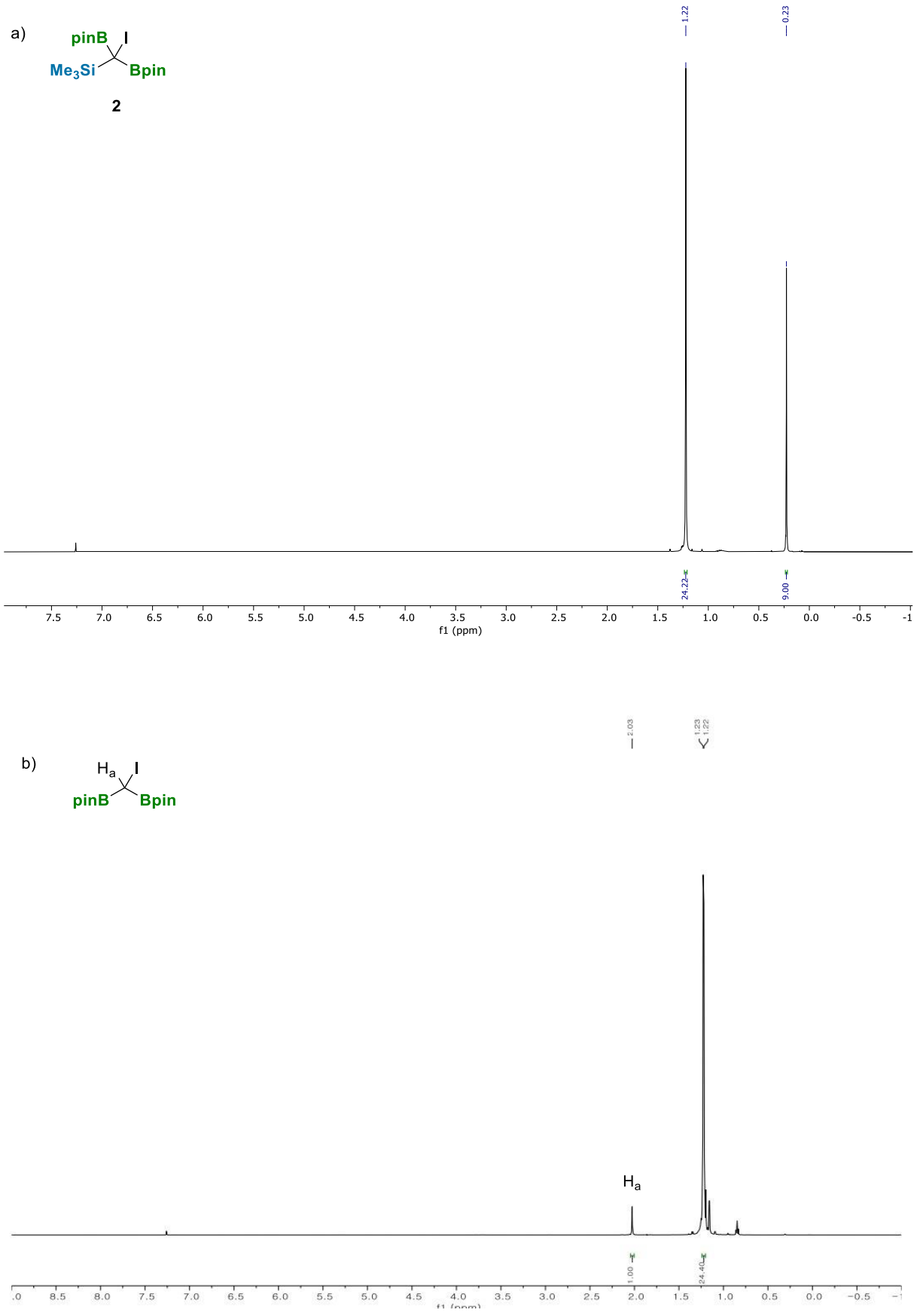
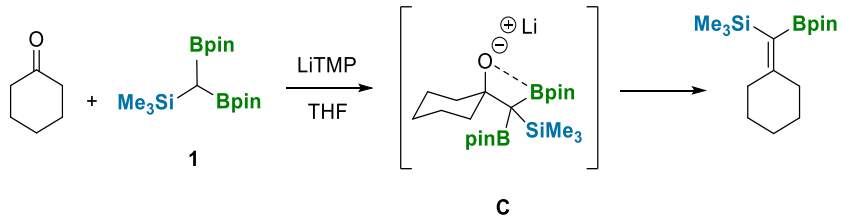



**Figure 3.** a) $^{1}$H NMR of IC(Bpin)$_2$(SiMe$_3$) (**2**). b) $^{1}$H NMR of ICH(Bpin)$_2$ from reference 11.

The difference between the two compounds is the presence of the trimethylsilyl group in compound **2**, instead of proton $H_a$ in $ICH(Bpin)_2$, showing a signal that appears as a singlet around 0.23 ppm that integrates nine protons, in agreement with the electron donor properties of the trimethylsilyl group. On the other hand, proton $H_a$ of the tertiary carbon of $ICH(Bpin)_2$ appears as a singlet at 2.03 ppm due to the deshielding promoted by the electron withdrawing effect of iodine.

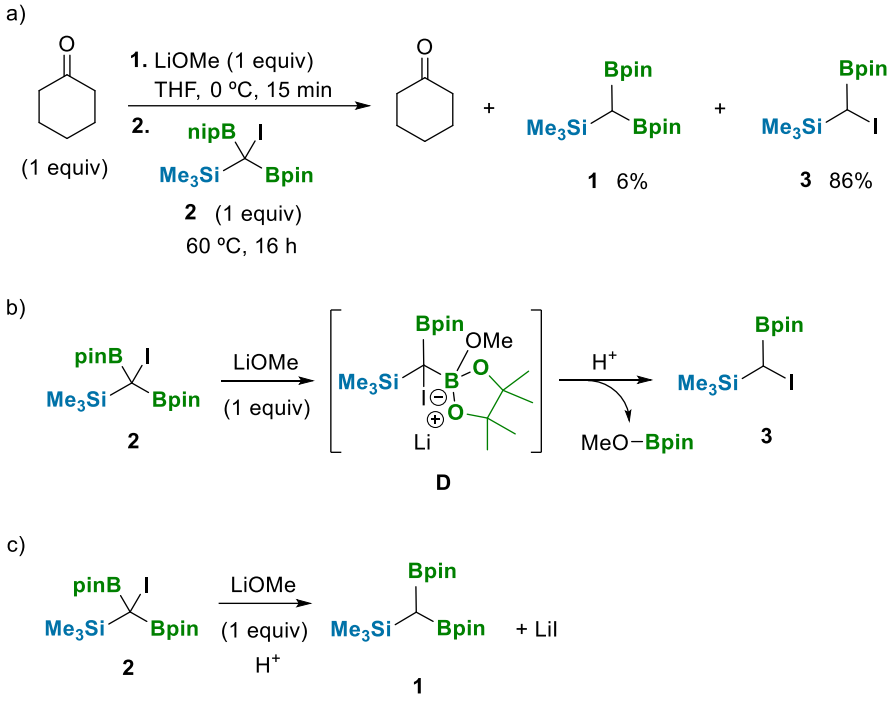
The next approach was aimed to explore the influence of different bases on the reactivity of $IC(Bpin)_2(SiMe_3)$ (**2**) with cyclohexanone, since the research group had previous experience on the use of LiTMP to deprotonate $HC(Bpin)_2(SiMe_3)$ (**1**) to react with cyclohexanone to perform the boron-Wittig reaction (Scheme 7).[8] Furthermore, cyclohexanone was also selected as the model ketone for all the experiments carried out because it is the simplest symmetrical cyclic ketone, which reduces the number of possible products in the reaction and facilitates and simplifies the purification of the reaction crudes. On the other hand, its high vapour pressure presents a challenge, as unreacted cyclohexanone can be easily evaporated in the rotatory evaporator during the reaction work-up.




1 C

**Scheme 7**. Reactivity of diborylmethylsilane **1** with cyclohexanone, in the presence of LiTMP.

Several lithiated bases have been selected to study the reactivity of cyclohexanone with **2**, such as LiOMe, LiMe, Li$^t$Bu, LiTMP and lithium diisopropylamide (LDA). Scheme 8a shows the reactivity of cyclohexanone with LiOMe, followed by the addition of reagent $IC(Bpin)_2(SiMe_3)$ (**2**) in tetrahydrofuran (THF). As it can be seen, the cyclohexanone did not react but the iodo-diborylmethylsilane **2** was mainly transformed into iodo-borylmethylsilane **3** and into diborylmethylsilane **1**. Compound **3** was obtained as a consequence of the favored methoxy deborylative pathway (Scheme 8b), where a methoxide anion attacks one of the boryl moieties due to the high oxophilicity, forming a boron ”ate” complex **D**. The formation of compound **1** suggests the iodide abstraction from **2** by the base LiOMe to form the highly stable LiI, and eventual protonation sequence along the work up (Scheme 8c).




**Scheme 8.** a) Reactivity of $IC(Bpin)_2(SiMe_3)$ (**2**) with cyclohexanone, in the presence of LiOMe. The NMR yield was calculated using naphthalene as an internal standard. b) Deborylation of compound **2** and formation of iodo-borylmethylsilane **3**. c) Iodide abstraction from **2** and formation of diborylmethylsilane **1**.

Compound **3** has been isolated for the first time in this work, and it was characterized *via* NMR spectroscopy. The $^1H$ NMR spectrum of iodo-borylmethylsilane **3** is depicted in Figure 4a, and can be compared with the $^1H$ NMR spectrum of compound **1** which is shown in Figure 4b. Structurally, the two compounds differ in the replacement of one of the pinacol boryl moieties by an iodine atom, which has important consequences in the electronic environment around the proton bound to the tertiary carbon. Due to its high electronegativity, the iodine atom in iodo-borylmethylsilane **3** deshields proton $H_b$ due to the inductive effect, which appears in the $^1H$ NMR spectrum as a singlet that integrates one proton at 1.85 ppm. On the other hand, the presence of the boryl group in diborylmethylsilane **1** instead of an iodine atom, causes proton $H_c$ to show more upfield. For this reason, proton $H_c$ in compound **1** is depicted as a singlet that integrates one proton at 0.30 ppm.

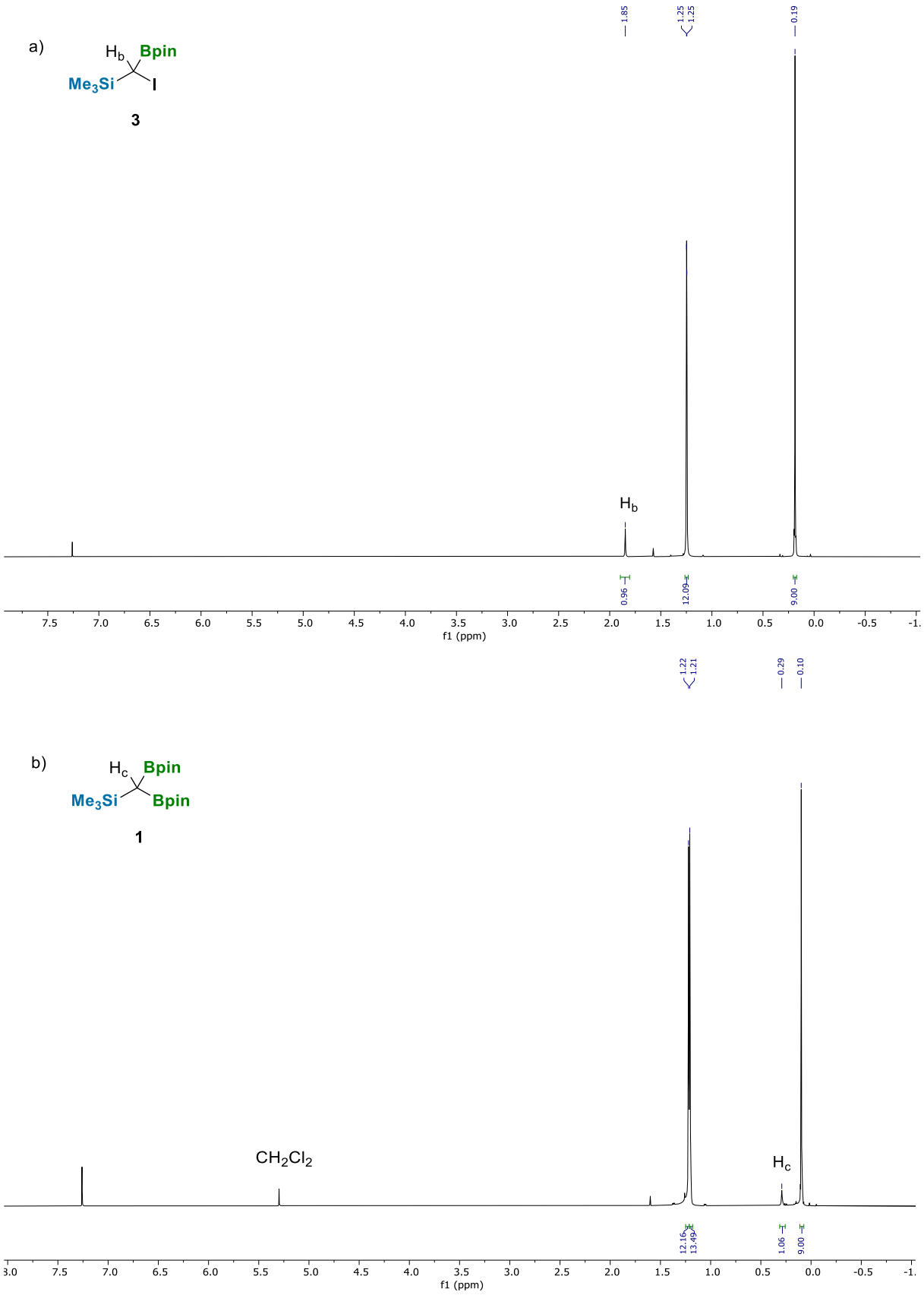
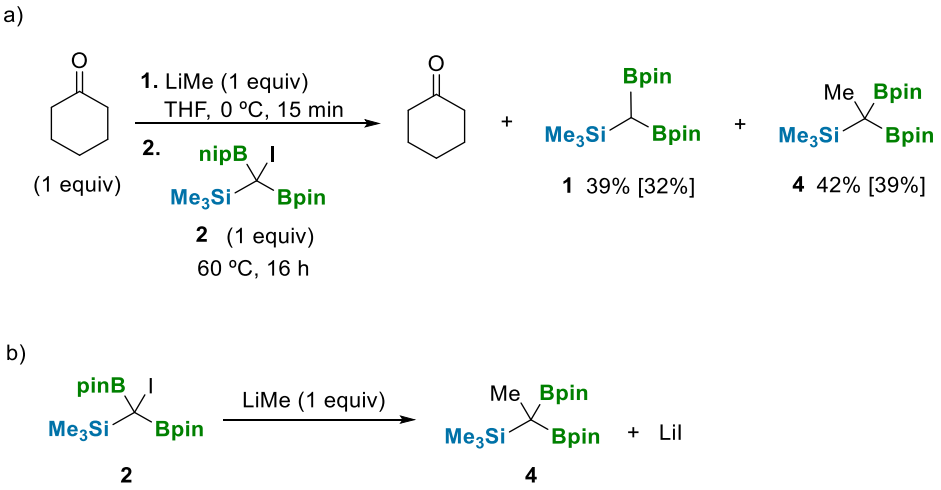



**Figure 4.** a) $^{1}$H NMR of iodo-borylsilylmethane **3**. b) $^{1}$H NMR of diborylsilylmethane **1**.

The following planned reaction involved the study of the influence of another lithiated base, LiMe, on the reactivity between cyclohexanone and reagent IC(Bpin)$_2$(SiMe$_3$) (**2**), using THF as solvent. Following the same general procedure described in the experimental part of the manuscript, it was observed that cyclohexanone did not react either, but the iodo-diborylmethylsilane **2** was transformed into two related products (Scheme 9a). The formation of compound **1** was quantified in 39% by NMR, and was isolated in 32% yield, suggesting the iodide abstraction from **2** by the base LiMe, and subsequent protonation sequence along the reaction work up. Interestingly, the formation of product (1-iodo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)trimethylsilane (**4**) was quantified in 42% NMR yield, and was isolated in 39% yield, potentially due to the methylation sequence of compound **2** *via* an $S_N2$ mechanism (Scheme 9b).




**Scheme 9.** a) Reactivity of IC(Bpin)$_2$(SiMe$_3$) (**2**) with cyclohexanone, in the presence of LiMe. The NMR yield was calculated using naphthalene as an internal standard, and the isolated yield is shown in brackets. b) Methylation of iodo-diborylmethylsilane **2** with LiMe.

Compound **4** was isolated for the first time in this work, and was characterized *via* NMR spectroscopy. The $^1$H NMR is shown in Figure 5a, and can be compared with the $^1$H NMR spectrum of analogue compound MeC(Bpin)$_2$(SiPhMe$_2$), which is shown in Figure 5b.[6] The phenyl moiety present in the silane group of MeC(Bpin)$_2$(SiPhMe$_2$) can be identified in the $^1$H NMR spectrum above 7 ppm in Figure 5b. The phenyl group also slightly modifies the electron environment around the protons of the two methyl substituents of the PhMe$_2$Si group, which show as a singlet that integrates six protons at 0.43 ppm, whereas the protons of the methyl moieties of the Me$_3$Si group of compound **4** appear more shielded, as a singlet that integrates nine protons at 0.07 ppm (Figure 5a).

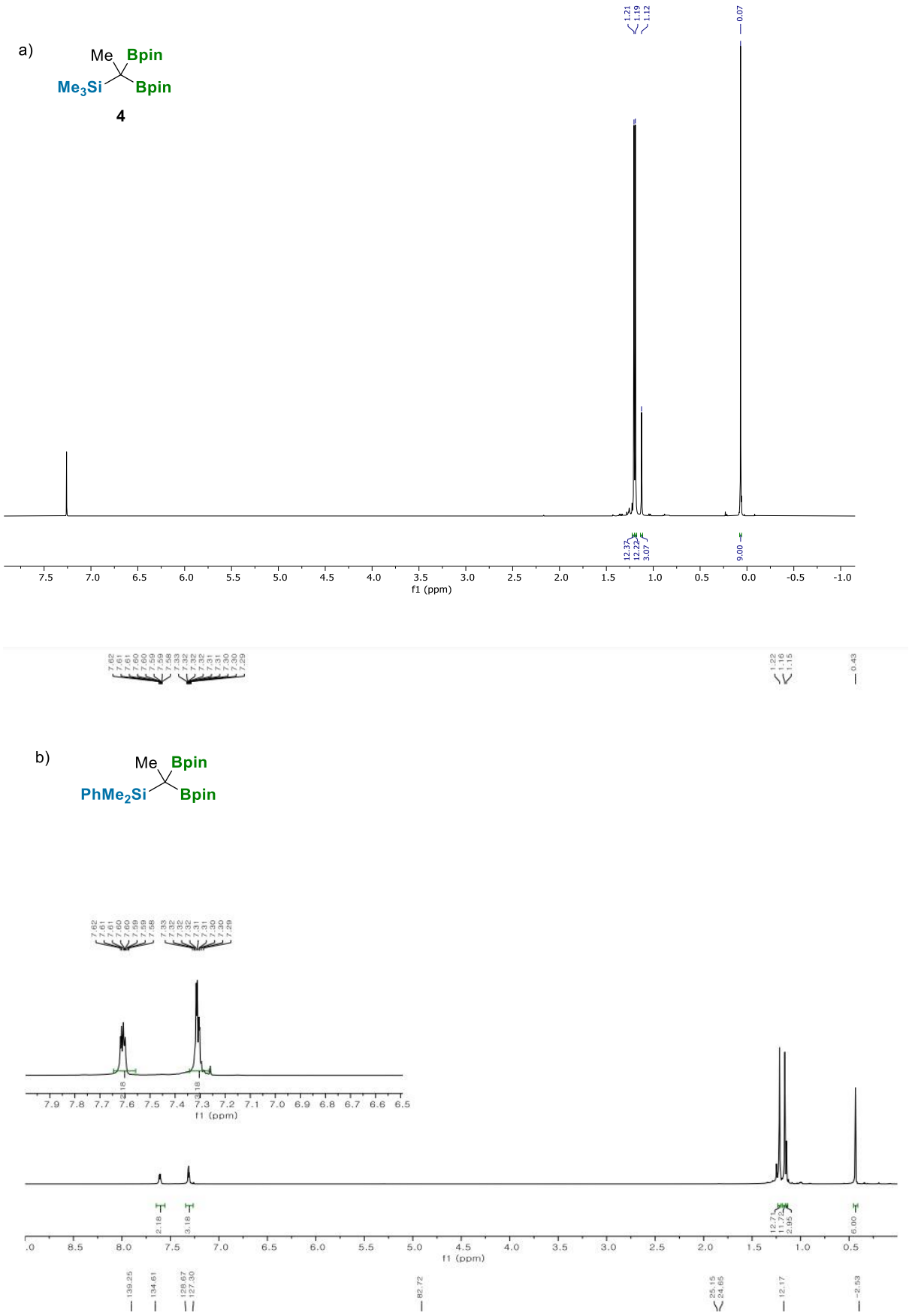
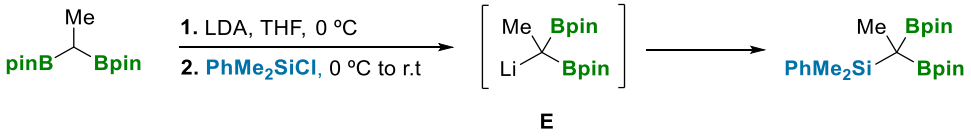



**Figure 5.** a) $^{1}$H NMR of MeC(Bpin)$_2$(SiMe$_3$) (**4**). b) $^{1}$H NMR of MeC(Bpin)$_2$(SiPhMe$_2$) from reference 6.

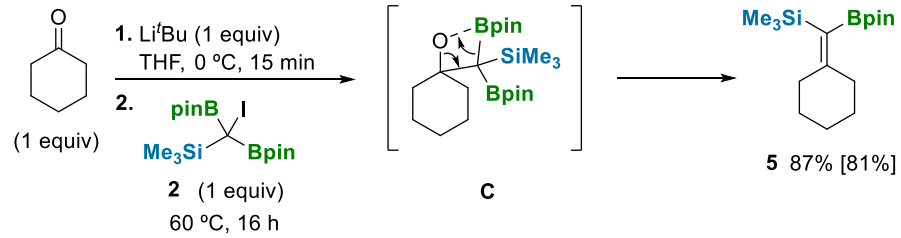
Compound MeC(Bpin)$_2$(SiPhMe$_2$) has been synthesized by Cho and co-workers following a different synthetic methodology.[6] The authors formed the diborylmethide salt **E** *in situ* by reaction between LDA and 1,1-diborylethane, to which they added the corresponding silyl chloride ClSiPhMe$_2$. Subsequently, the diborylmethide salt **E** attacked the silyl chloride *via* an $S_N2$ mechanism forming MeC(Bpin)$_2$(SiPhMe$_2$) as shown in Scheme 10.




**Scheme 10.** Preparation of MeC(Bpin)$_2$(SiPhMe$_2$) by Cho and co-workers.[6]

Afterwards, the addition of Li$^t$Bu to the reaction between cyclohexanone and reagent iodo-diborylmethylsilane **2** was studied, using THF as solvent. The use of Li$^t$Bu made a significant change on the reaction outcome since the cyclohexanone transformation towards the boron-Wittig reaction product **5** was principally observed in 87% NMR yield, and was isolated in 81% yield. It is suggested that the formation of the $S_N2$ product, $^t$BuC(Bpin)$_2$(SiMe$_3$), is not favoured due to the bulkiness of the substituents around iodo-diborylmethylsilane **2** and the bulkiness of the nucleophile itself, while the nucleophilic substitution is feasible when LiMe is used, as the nucleophile is smaller in size and therefore has lesser steric impediments.

On the other hand, it is suggested that the iodide abstraction from **2** takes place efficiently with Li$^t$Bu, and the corresponding carbanion reacts with the cyclohexanone to give intermediate **C** that evolves towards the boron-Wittig reaction product **5** as shown in Scheme 11.




**Scheme 11.** Reactivity of IC(Bpin)$_2$(SiMe$_3$) (**2**) with cyclohexanone, in the presence of Li$^t$Bu. The NMR yield was calculated using naphthalene as an internal standard, and the isolated yield is shown in brackets.

The characterization of product **5** was conducted by NMR spectroscopy. The $^1$H NMR spectrum obtained was in agreement with the data reported in the literature (Figure 6),[8] confirming that the product obtained is the one from the boron-Wittig reaction.

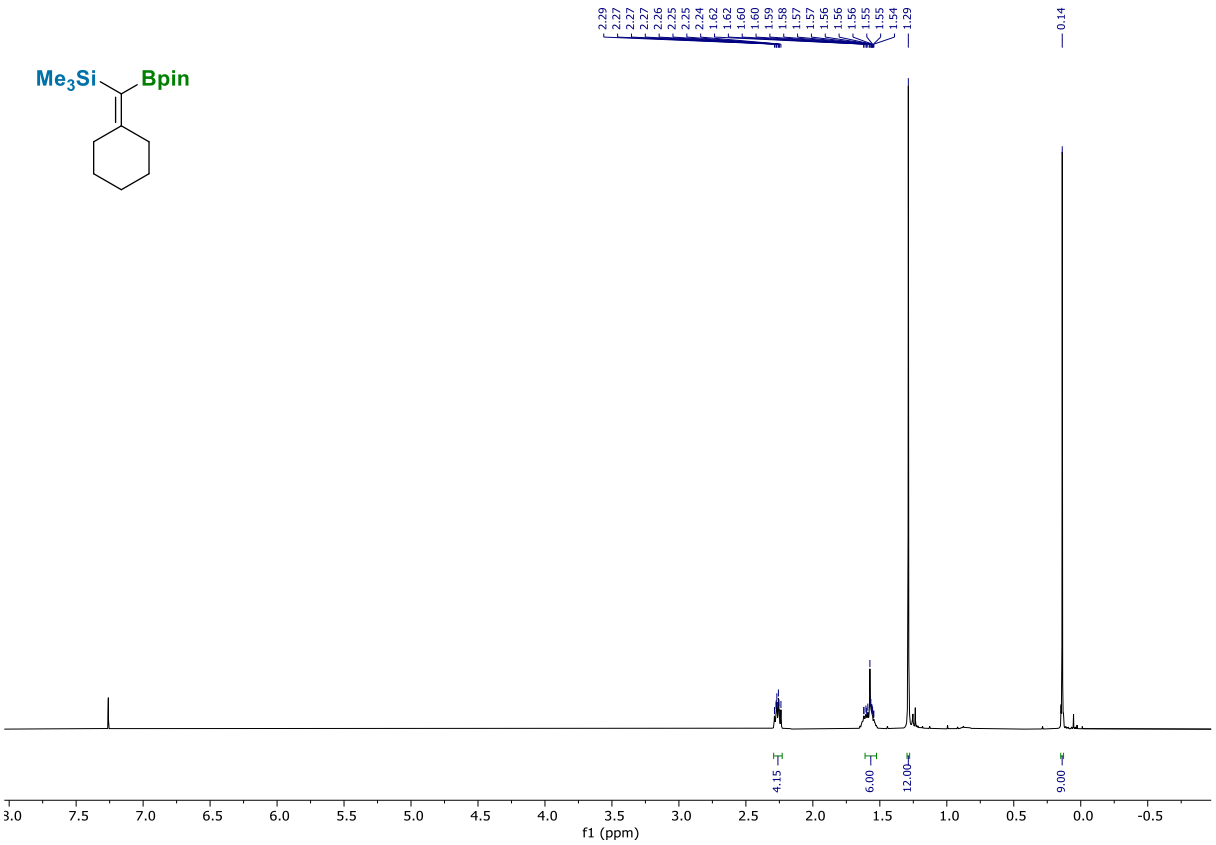
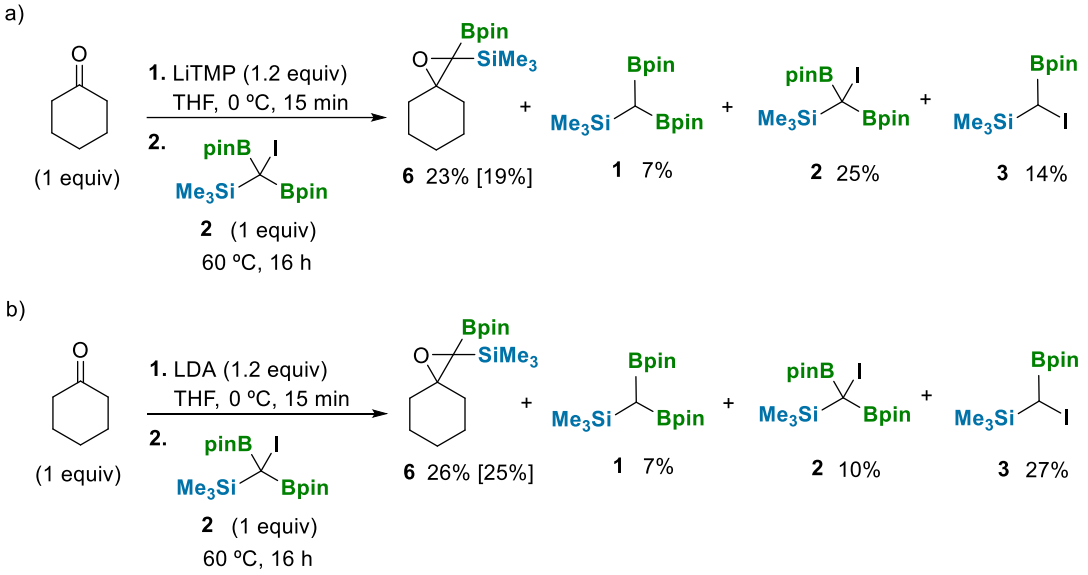



**Figure 6.** $^{1}$H NMR spectrum of product **5** synthesized in this work.

The next lithiated base that was used was LiTMP, and surprisingly, the reaction between cyclohexanone and reagent $IC(Bpin)_2(SiMe_3)$ (**2**), in $Et_2O$ as solvent, generated a new product that was identified as a spiro-epoxy derivative, trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-oxaspiro[2.5]octan-2-yl)silane (**6**), which was observed in 23% NMR yield, and was isolated in 19% yield (Scheme 12a). In addition to the transformation of cyclohexanone into product **6**, unreacted iodo-diborylmethylsilane **2** was also observed in 25% with respect to the other byproducts, as well as the corresponding protodeborated compound **3** in 14% and some of the protodeiodinated compound **1** in 7%. The same reaction was also tested, but using LDA as a lithiated base, under the same conditions as with LiTMP, and the formation of the spiro-epoxy derivative **6** was also observed, as well as the protodeborated product **3** and the protodeiodinated **1** byproducts, but in different proportions, which are shown in Scheme 12b.




**Scheme 12.** a) Reactivity of $IC(Bpin)_2(SiMe_3)$ (**2**) with cyclohexanone, in the presence of LiTMP. b) Reactivity of $IC(Bpin)_2(SiMe_3)$ (**2**) with cyclohexanone, in the presence of LDA. The NMR yield was calculated using naphthalene as an internal standard, and the isolated yield is shown in brackets.

The characterization of the new product **6** was established *via* NMR spectroscopy. The $^1$H NMR spectrum of said product is shown in Figure 7a, and for comparison, Figure 7b depicts the $^1$H NMR data for 1-oxaspiro[2.5]octane, which is another spiro-epoxy derivative similar to compound **6** that was synthesized by Majerić and co-workers.[12]

The difference between the two molecules is the presence of a trimethylsilyl and pinacol boryl group in the epoxide of compound **6**. Protons $H_d$ of 1-oxaspiro[2.5]octane appear deshielded due to the inductive effect caused by the oxygen atom of the epoxide, and they show as a singlet that integrates two protons at 2.59 ppm (Figure 7b). This signal does not appear in the spectrum of the synthesized spiro-epoxide **6**, but the other signals corresponding to the protons of the cyclohexyl moiety are present, between 1.50 and 1.75 ppm, as well as the signals of the protons of the pinacol boryl and trimethylsilyl group, meaning that the product of the reaction involves the coupling of the cyclohexanone reagent and the iodo-diborylmethylsilane **2**.

Considering that both lithiated bases, LiTMP and LDA, favoured the formation of the new spiro-epoxy derivative **6** in a comparative way, the use of LiTMP as base was maintained for the remaining experiments. Moreover, other reaction conditions were altered to study their influence on the reaction outcome, such as the excess of both ketone and base.

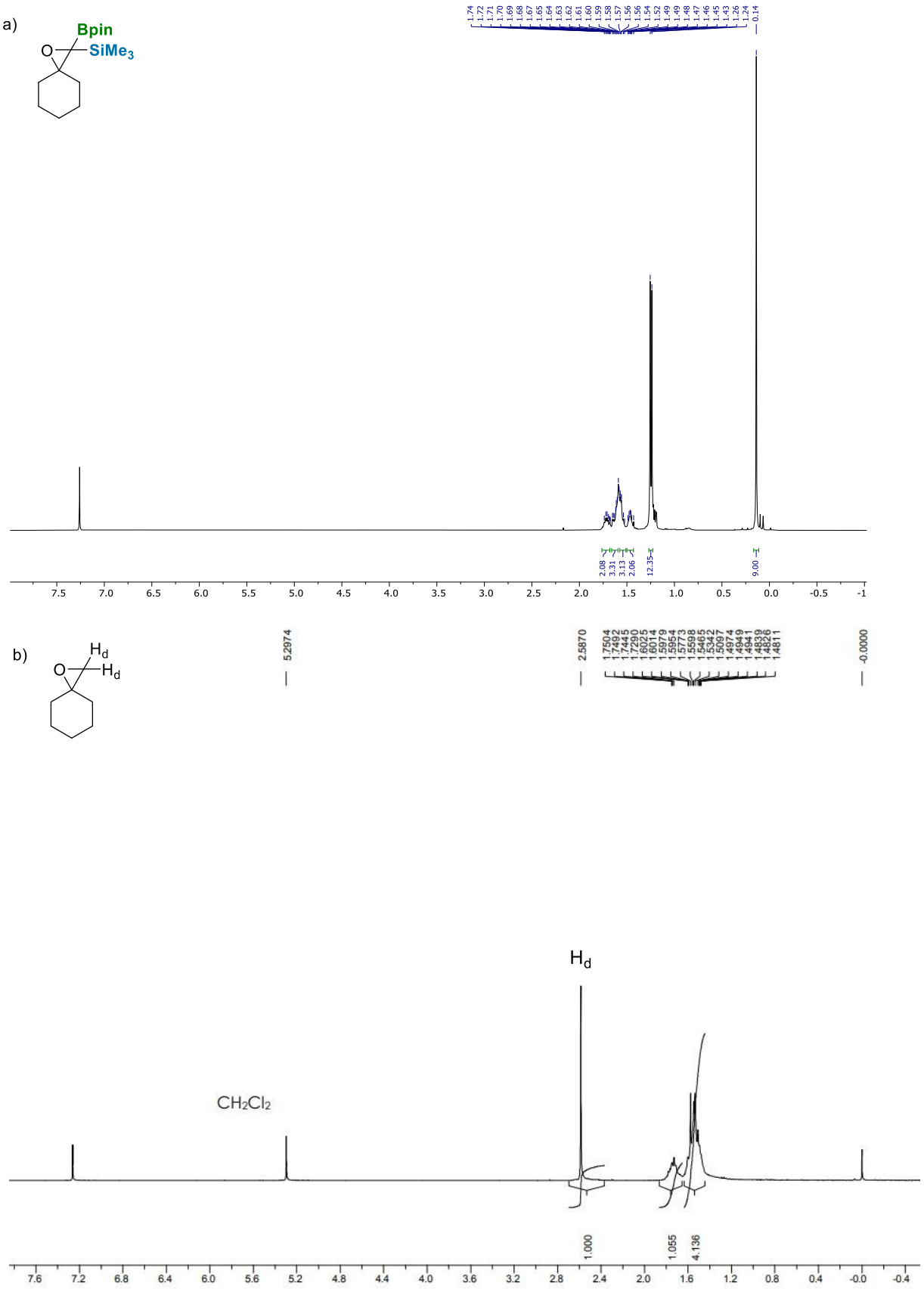
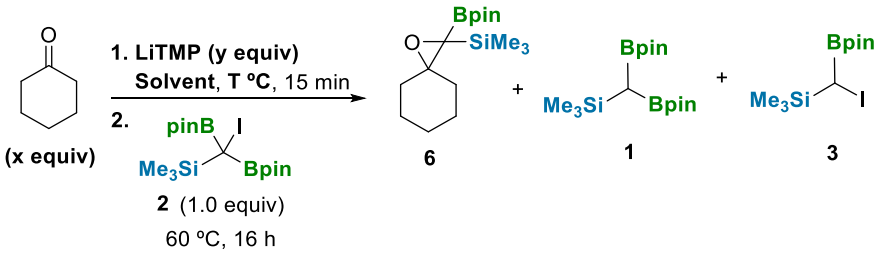



**Figure 7.** a) $^{1}$H NMR spectrum of trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-oxaspiro[2.5]octan-2-yl)silane (**6**). b) $^{1}$H NMR spectrum of 1-oxaspiro[2.5]octane from reference 12.

The effect of these reaction conditions on the proportion of the final products is collected in Table 1. Entries 1 and 2 of Table 1 show the influence of an excess of ketone and LiTMP, using $Et_2O$ as solvent, since iodo-diborylmethylsilane **2** is almost consumed completely when an excess of base is present. When $Et_2O$ was replaced by THF as solvent, the formation of the new spiro-epoxy derivative **6** was also observed, which was favoured more when an excess of both ketone and LiTMP were used, as shown in entries 3 and 4 of table 1. Entry 5 of table 1 shows the effect of the temperature on the reaction products, where it was observed that mixing the ketone and LiTMP at -78 °C, instead of 0 °C, did not favour the formation of the spiro-epoxy derivative **6**. Finally, as shown in entry 6 of table 1, a relative excess of cyclohexanone with respect to LiTMP did not contribute to promote the formation of product **6**, although iodo-diborylmethylsilane **2** was completely consumed.

**Table 1.** Synthesis of spiro-epoxy **6** from reaction of iodo-diborymethylsilane **2** with cyclohexanone, in the presence LiTMP. NMR yields were calculated using naphthalene as an internal standard and isolated yields are shown in brackets.

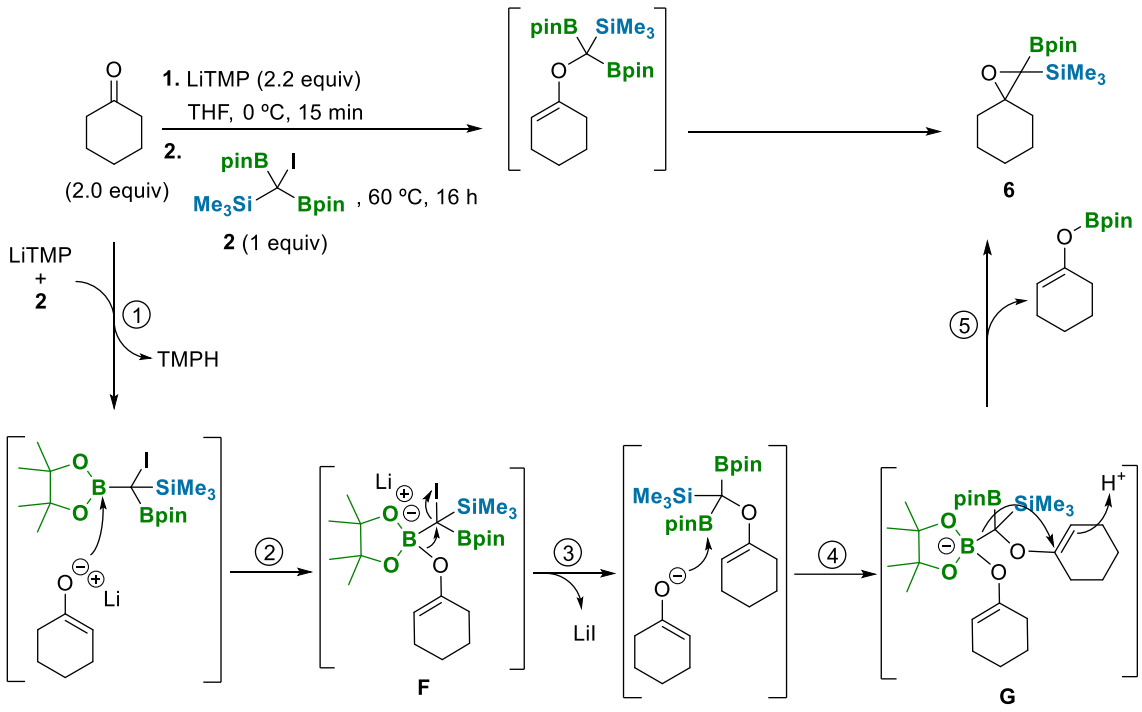



| Entry | T (ºC) | Solvent | (x equiv) | LiTMP (y equiv) | Yields | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 2 | 6 | 1 | 3 |
| **1** | 0 | $Et_2O$ | 1.0 | 1.2 | 25% | 23% [19%] | 7% | 14% |
| **2** | 0 | $Et_2O$ | 2.0 | 2.2 | 5% | 27% | 3% | 40% |
| **3** | 0 | THF | 1.0 | 1.2 | 33% | 17% | 26% | 24% |
| **4** | 0 | THF | 2.0 | 2.2 | 1% | 35% | 23% | 36% |
| **5** | -78 | THF | 2.0 | 2.2 | 0% | 24% | 46% | 16% |
| **6** | 0 | THF | 3.0 | 2.2 | 0% | 20% | 38% | 25% |

A plausible mechanism for the formation of the spiro-epoxy derivative **6** can be proposed with all the data collected. According to the data from Table 1, the formation of compound **6** is promoted the most when the formation of the cyclohexanone enolate takes place at 0 ºC, when THF is used as a solvent, and most importantly, when an excess of both cyclohexanone and LiTMP are used with respect to iodo-diborylmethylsilane **2**, which could mean that two molecules of cyclohexanone enolate react per each molecule of

iodo-diborylmethylsilane **2**. The slight excess of base with respect to the ketone is simply to ensure that all the cyclohexanone is converted into its enolate. Furthermore, the potential of compound **2** to undergo Matteson 1,2-rearrangements[10] in front of a nucleophile, such as cyclohexanone enolate in this case, has led to the proposal of the five-step mechanism shown in Scheme 13.

The first step of the mechanism consists of the deprotonation of cyclohexanone by LiTMP, where the cyclohexanone enolate is formed, thus generating the nucleophile of the reaction. Consequently, in the second step, when iodo-diborylmethylsilane **2** is added to the reaction, the enolate readily attacks one of the boryl groups due to their oxophilicity, generating a boron "ate" complex. This intermediate undergoes a Matteson 1,2-rearrangement in the third step due to the iodine atom in the α-carbon of the alkylboronic ester **F**, which is expelled, forming lithium iodide, which acts as the driving force of this step.




**Scheme 13**. Proposed mechanism for the formation of the spiro-epoxy derivative **6**.

The excess of the added cyclohexanone now plays a key role, as a second equivalent of cyclohexanone enolate attacks one of the boryl groups again, forming another boron "ate" complex **G**. However, the lack of a suitable leaving group in the α-carbon does not allow for a second Matteson rearrangement to take place. For this reason, it is believed that one of the pinacol boryl groups is expelled in the fifth step of the mechanism, in the form of a stable boronic ester. Furthermore, it is believed that this is the driving force of the formation of the epoxide, which also requires a protic source. This proton could come

from the reaction work-up, where the Schlenk flask where the reaction has been carried out is rinsed several times with solvents such as dichloromethane and diethyl ether, which have not been properly dried and could contain moisture that could drive the protonation of intermediate **F**. If this was the case, it is believed that the efficiency of the reaction could be significantly improved by adding a few drops of a weak organic acid such as p-toluenesulfonic acid, either before stopping the reaction or in the reaction work-up. Nevertheless, this hypothesis should be experimentally tested to observe if its effect on the yield of the reaction is in fact significant.

This pathway is only a proposal, and a parallel computational study of the reaction mechanism should be carried out to assess the free energy of the intermediates involved as well as the transition states that link them, as a complement of the experimental data provided.

# 5. EXPERIMENTAL PART

## 5.1 General considerations

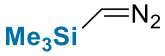
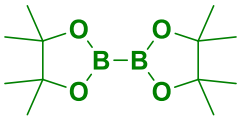
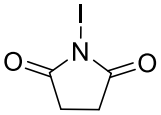
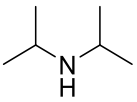
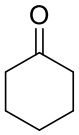
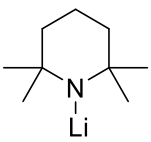
Solvents and reagents were obtained from commercial suppliers, such as Sigma-Aldrich Inc., Apollo Scientific, Fluorochem, Abcr GmbH, Alfa Aesar, Acros Organics or TCI Chemicals; and were dried and/or purified (if needed) by standard procedures.[13] Bis(pinacolato)diboron ($B_2pin_2$) was obtained as a generous donation from Dalian Allychem Co., and was used without further purification. All air-sensitive reactions and procedures were conducted in oven dried glassware under an inert atmosphere of argon and using Schlenk-type techniques. Flash chromatography purification procedures were performed on standard silica gel (Merck Kiesegel 60 Å, 230-400 mesh particle size). Thin Layer Chromatography analyses (TLC) were performed on Merck Kiesegel 60 F254 and were developed using standard visualizing agents such as potassium permanganate and. NMR spectra were recorded at a Varian 400 spectrometer. $^{1}$H NMR and $^{13}$C NMR chemical shifts (δ) are reported in ppm with the solvent residual signals as reference internal standard (CDCl3 = 7.26 ppm 1H and 77.16 ppm 13C). $^{11}$B NMR chemical shifts (δ) are reported in ppm relative to BF3·Et2O. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constants (Hz), integration). High Resolution Mass Spectra (HRMS) were recorded using a BIOTOF II TOF mass spectrometer from Bruker with APCI or EI interface that is located at the Unidade de Espectrometría de Masas e Proteómica of the Universidade de Santiago de Compostela. GC-MS analyses were performed on an 8860 GC System with a 5977B GC/MSD from Agilent Technologies equipped with a capillary column HP-5MS Ultra Inert (30 m, 0.25 mm i.d., 0.25 μm thickness) and using He as the carrier gas.

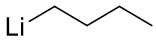
## 5.2 Safety precautions

### 5.2.1 Reagents

All the reagents used in this work have been manipulated using nitrile gloves, safety goggles and a laboratory coat, inside a fume hood with appropriate ventilation.

**Table 2**. Manipulation and characteristics of toxicity of the most representative reagents used in this work.

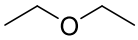
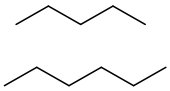
| | |
|---|---|
|  <br>(diazomethyl)trimethylsilane | $C_4H_{10}N_2Si$. CAS: 18107-18-1. MW: 114.22 g/mol. Molarity: 2M in hexanes. This reagent was used inside a nitrogen-filled glove box.<br>  |
|  <br>bis(pinacolato)diboron | $C_{12}H_{24}B_2O_4$. CAS: 73183-34-3. MW: 253.94 g/mol. Purity: 99%. |
|  <br>*N*-iodosuccinimide | $C_4H_4INO_2$. CAS: 516-12-1. MW: 224.98 g/mol. Purity: 95%.<br>  |
|  <br>diisopropylamine | $C_6H_{15}N$. CAS: 108-18-9. MW: 101.19 g/mol. Purity: ≥99.5%. Density: 0.722 g/mL. Flammable, toxic, corrosive.<br>  |
|  <br>cyclohexanone | $C_6H_{10}O$. CAS: 108-94-1. MW: 98.14 g/mol. Purity: ≥99.0%. Density: 0.948 g/mL.<br>  |
|  <br>lithium 2,2,6,6-tetramethylpiperidide | $C_9H_{18}LiN$. CAS: 38227-87-1. MW: 147.19 g/mol. Purity: 97%. This reagent was used inside a nitrogen-filled glove box.<br>  |

| | |
|---|---|
| Li—$OCH_3$<br>lithium methoxide | $CH_3OLi$. CAS: 865-34-9. MW: 37.97 g/mol.<br>Purity: 98%.<br>  |
| Li—$CH_3$<br>methyllithium | $CH_3Li$. CAS: 917-54-4. MW: 21.98 g/mol.<br>Molarity: 1.6M in diethyl ether. This reagent is contained inside an inert atmosphere.<br>  |
|  <br>*n*-butyllithium | $C_4H_9Li$. CAS: 109-72-8. MW: 64.06 g/mol.<br>Molarity: 2.5M in hexanes. This reagent is contained inside an inert atmosphere.<br>  |
|  <br>*tert*-butyllithium | $C_4H_9Li$. CAS: 594-19-4. MW: 64.06 g/mol.<br>Molarity: 1.7M in pentanes. This reagent is contained inside an inert atmosphere.<br>  |

### 5.2.2 Solvents

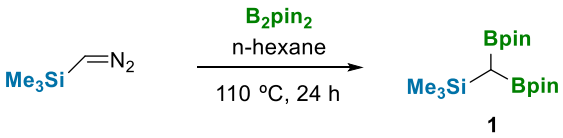
**Table 3**. Storage and characteristics of toxicity of the most representative solvents used in this work.

| | |
|---|---|
|  <br>tetrahydrofuran | $C_4H_8O$. CAS: 109-99-9. MW: 72.11 g/mol.<br>Purity: ≥99.9%. This solvent was stored with molecular sieves and was dried using a Solvent Purification System (SPS).<br>  |

| | |
|---|---|
| $CH_2Cl_2$<br>dichloromethane | $CH_2Cl_2$. CAS: 75-09-2. MW: 84.93 g/mol. Purity: ≥99.8%. This solvent was stored inside a glass container.<br>  |
|  <br>diethyl ether | $C_4H_{10}O$. CAS: 60-29-7. MW: 74.12 g/mol. Purity: ≥99.0%. This solvent was dried using a Solvent Purification System (SPS).<br>  |
|  <br>petroleum ether | CAS: 101316-46-5. Density: 0.640-0.655 g/mL at 20 ºC. This solvent was stored inside a glass container.<br>  |

## 5.3 General procedures

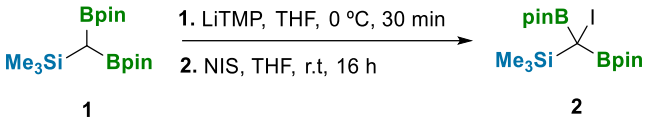
**General procedure for the synthesis of (bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane** (**1**).




**1**

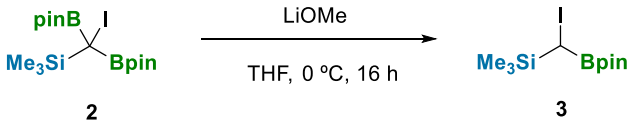
An oven-dried 100 mL Teflon screw-cap Schlenk flask, equipped with a magnetic stir bar, was charged with bis(pinacolato) diboron (10.00 mmol, 1.0 equiv). Next, inside the glove box, 10 mL of a 2.0 M solution of (trimethylsilyl)diazomethane in n-hexane (20.00 mmol, 2.0 equiv) were added dropwise to the Schlenk flask containing the diboron reagent. After stirring the mixture in the glove box for 5 minutes, the Schlenk flask was sealed and heated to 110 ºC for 24 hours under constant stirring. Afterwards, the reaction was allowed to cool to room temperature, and the solvent was gently concentrated on a rotary evaporator. The resulting crude was purified by silica gel flash chromatography to afford the final product in 87% yield.

**General procedure for the synthesis of (iodobis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane** (**2**).



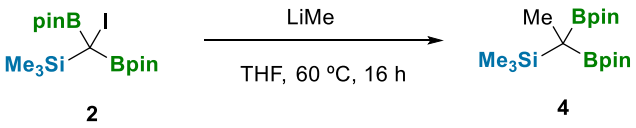

An oven-dried 100 mL Teflon screw-cap Schlenk flask, equipped with a magnetic stir bar, was charged with the diborylsilylmethane reagent (1.00 mmol, 1.0 equiv), to which, inside the glove box, LiTMP was added (1.20 mmol, 1.2 equiv). Then, 4 mL of dry THF were added to the flask, and the solution was homogenized by stirring for 30 minutes at 0 ºC inside an ice bath. Next, the solution was transferred *via* a cannula to a previously prepared Schlenk flask containing a solution of *N*-iodosuccinimide (3.00 mmol, 3.0 equiv) in 4 mL of dry THF, covered in aluminum foil to avoid the influence of external light, and the reaction was left to occur for the following 16 hours. Afterwards, the reaction crude was quenched with sodium thiosulfate and extracted with diethyl ether. The organic phase was treated with 10% HCl and brine, in this order, and was dried using magnesium sulfate, filtered and concentrated in the rotary evaporator. The final product was purified and isolated using silica gel flash chromatography in 67% yield.

**General procedure for the synthesis of (iodo(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane** (**3**).



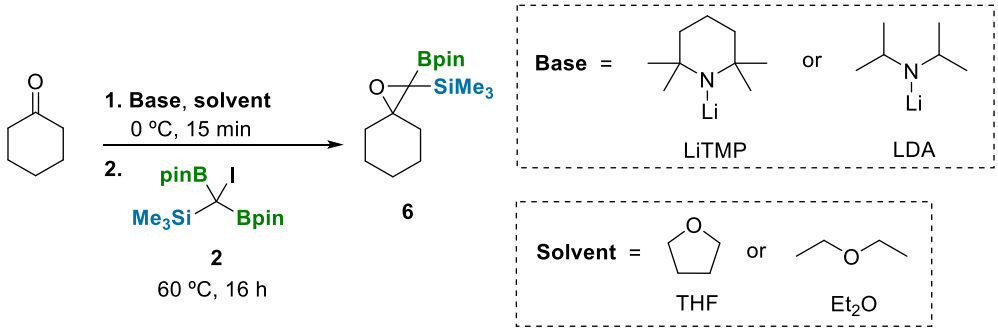

An oven-dried 100 mL Teflon screw-cap Schlenk flask, equipped with a magnetic stir bar, was charged with lithium methoxide (0.50 mmol, 1.0 equiv), which was solubilized in 1 mL of dry THF. Then, the iodo-diborylsilylmethane reagent (0.50 mmol, 1.0 equiv) was added to the solution under argon and constant stirring at 0 ºC inside an ice bath. The mixture was left to react for 16 hours, and next, the solvent was gently concentrated on a rotary evaporator. The reaction crude was purified using silica gel flash chromatography, and the final product was successfully isolated in 84% yield.

**General procedure for the synthesis of (1,1-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)trimethylsilane** (**4**).




An oven-dried Teflon screw-cap Schlenk flask, equipped with a magnetic stirring bar, was charged with iodo-diborylmethylsilane **2** (0.10 mmol, 1.0 equiv), which was solubilized in 1 mL of dry THF. Subsequently, LiMe (0.10 mmol, 1.0 equiv) was added under argon and constant stirring at 60 ºC for 16 hours. Afterwards, the solvent was evaporated in a rotary evaporator, and the reaction crude was purified using silica gel flash chromatography. The final product **4** was isolated in 39% yield.

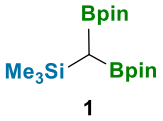
**General procedure for the synthesis of trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-oxaspiro[2.5]octan-2-yl)silane** (**6**).




An oven-dried Teflon screw-cap Schlenk flask, equipped with a magnetic stirring bar, was charged with **base** (0.30-0.55 mmol, 1.2-2.2 equiv), which was solubilized in 1 mL of dry **solvent**. Afterwards, cyclohexanone (0.50-0.75 mmol, 2.0-3.0 equiv) was added to the same Schlenk flask using a Hamilton syringe under argon and constant stirring at 0 ºC inside an ice bath and the mixture was left to react for approximately 15 minutes. Subsequently, $IC(Bpin)_2(SiMe_3)$ **2** (0.25 mmol, 1 equiv) was added to the reaction mixture, which was heated up to 60 ºC inside an oil bath, and the reaction was left overnight for around 16 hours. Following this, the solvent was concentrated in a rotary evaporator, and the reaction crude was purified using silica gel flash chromatography, with which the product was isolated in 35% yield.

## 5.4 Spectral data

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



**1**

Purified by flash column chromatography (petroleum ether: diethyl ether =150:10) yielded **1** (87%, 2.96 mg), as a pale yellowish solid.

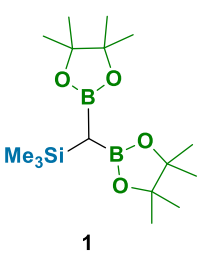
**$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 1.22 (s, 12H), 1.21 (s, 12H), 0.29 (s, 1H), 0.10 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 82.8, 25.1, 24.7, 0.7.

**$^{11}$B NMR** ($CDCl_3$, 129 MHz) δ 33.6.

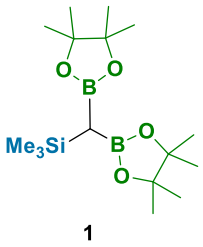
These data are in agreement with those reported in the literature.[8]

**$^{1}$H NMR spectrum.**



**1**

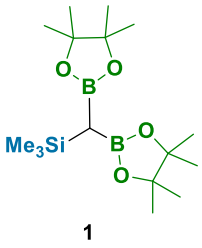
**$^{13}$C NMR spectrum.**




**1**

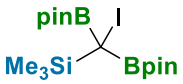



**$^{11}$B NMR spectrum.**




**1**

**(Iodo-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane** (**2**).




**2**

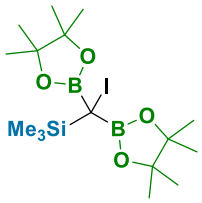
Purified by flash column chromatography (petroleum ether: diethyl ether = 10:1) yielded **2** (67%, 310.12 mg), as a yellowish solid.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 1.23 (s, 24H), 0.23 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 84.1, 24.8, 24.6, -0.2.

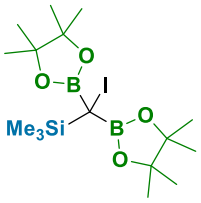
**$^{11}$B NMR** ($CDCl_3$, 129 MHz) δ 33.0.

**$^{1}$H NMR spectrum.**




**2**

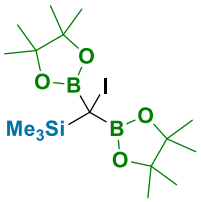
**$^{13}$C NMR spectrum.**




**2**

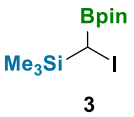



**$^{11}$B NMR spectrum.**




**2**

**Iodo-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane** (**3**).

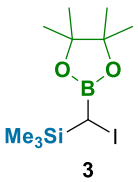



**3**

Purified by flash column chromatography (petroleum ether: diethyl ether = 200:1) yielded **3** (84%, 160.34 mg), as a pale-yellow solid.

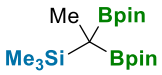
**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 1.84 (s, 1H), 1.24 (s, 12H), 0.18 (s, 9H).

**$^1$H NMR spectrum.**




**3**

**(1,1-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)trimethylsilane** (**4**).




**4**

Purified by flash column chromatography (petroleum ether: diethyl ether =150:10) yielded **4** (39%, 12.75 mg), as a white solid.

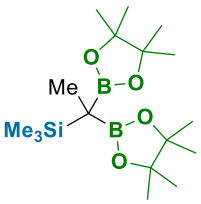
**$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 1.21 (s, 12H), 1.19 (s, 12H), 1.12 (s, 3H), 0.07 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 84.1, 26.6, 26.1, 13.4, 0.0.

**$^{11}$B NMR** ($CDCl_3$, 129 MHz) δ 34.0.

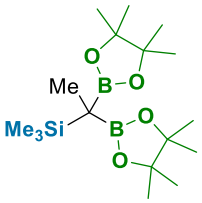
These data are in agreement with those reported in the literature.[6]

**$^{1}$H NMR spectrum.**




**4**

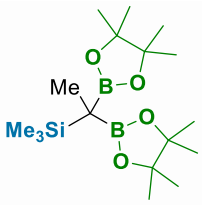
**$^{13}$C NMR spectrum.**




**4**

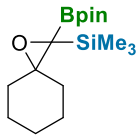



**$^{11}$B NMR spectrum.**




**4**

**Trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-oxaspiro[2.5]octan-2-yl)silane** (**6**).

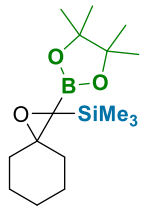



**6**

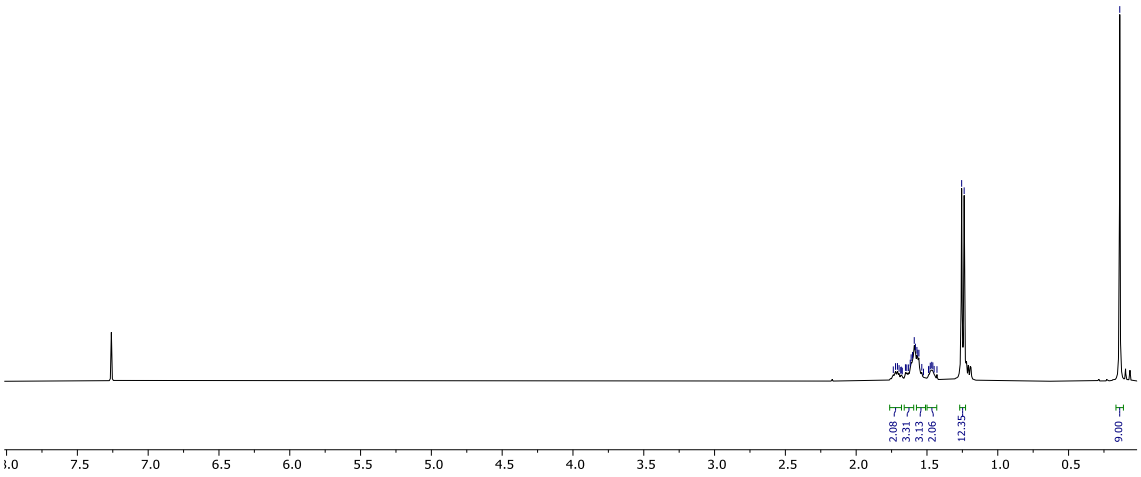
Purified by flash column chromatography (petroleum ether: diethyl ether = 25:1) yielded **6** (35%, 13.58 mg), as a yellowish oil.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 1.75 – 1.67 (m, 2H), 1.64 (dd, *J* = 9.3, 4.2 Hz, 3H), 1.57 (dd, *J* = 6.2, 3.6 Hz, 3H), 1.47 (m, 2H), 1.25 (s, 6H), 1.24 (s, 6H), 0.14 (s, 9H).
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 84.6, 67.4, 36.5, 34.4, 26.2, 26.1, 26.0, 25.9, 25.5, 0.0.
**$^{11}$B NMR** ($CDCl_3$, 129 MHz) δ 32.3.

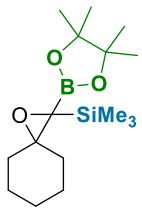
**$^{1}$H NMR spectrum.**




**6**

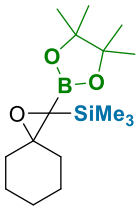
**$^{13}$C NMR spectrum.**




**6**




**$^{11}$B NMR spectrum.**




**6**

# 6. Conclusions

**English:**

The main focus of the present Bachelor's Thesis was aimed towards the synthesis of the novel reagent iodo-diborylmethylsilane **2** and the study of its reactivity in front of cyclohexanone. It is important to mention that the objectives planned ahead for this work have been accomplished, and the main conclusions are the following.

1. The new *gem*-diborylalkane compound $IC(Bpin)_2(SiMe_3)$ (**2**) has been successfully synthesized from diborylmethylsilane **1** and *N*-iodosuccinimide, and has been isolated in good yields.
2. Iodo-diborylmethylsilane **2** has been characterized using NMR spectroscopy.
3. The behavior of compound **2** in front of several lithiated bases and cyclohexanone has been studied in detail. Nitrogenated bases such as LDA and LiTMP have promoted the formation of a novel spiro-epoxy derivative **6**. On the other hand, oxygenated bases such as LiOMe have facilitated the deborylation of iodo-diborylmethylsilane **2** instead, evolving towards the formation of a new reagent, borylmethylsilane **3**. Additionally, lithiated hydrocarbons such as LiMe and Li$^t$Bu have favored the formation of other products, in the case of LiMe, the $S_N2$ product **4**, and in the case of Li$^t$Bu, the formation of the boron-Wittig product **5**, without the formation of the spiro-epoxy derivative **6**.
4. The homologative coupling between cyclohexanone and iodo-diborylmethylsilane **2** has been studied, where the formation of the novel spiro-epoxy derivative **6** has been observed. Compound **6** has been successfully isolated and characterized using NMR spectroscopy. Furthermore, a plausible mechanism for the formation of **6** has been proposed.

**Català:**

L'objectiu principal d'aquest treball de fi de grau és la síntesi del nou reactiu iodur de diborilmetilsilà **2** així com l'estudi de la seva reactivitat davant de la ciclohexanona. És important recalcar que els diversos objectius plantejats abans de la realització d'aquest treball han estat complerts, i les principals conclusions són les següents.

1. S'ha sintetitzat el nou reactiu *gem*-diborilalcà $IC(Bpin)_2(SiMe_3)$ (**2**) a partir del diborilmetilsilà **1** i la *N*-iodosuccinimida, el qual s'ha aïllat amb un bon rendiment.
2. S'ha caracteritzat el nou iodur de diborilmetilsilà **2** fent servir tècniques de caracterització com espectroscòpia RMN.
3. S'ha estudiat el comportament del producte **2** davant de bases litiades i de la ciclohexanona. S'ha observat que quan s'empren bases nitrogenades com la LDA o la LiTMP, es promou la formación d'un nou compost espiro-epoxi **6**. A més, quan s'han fet servir bases oxigenades com el LiOMe, es facilita la deborilació del compost **2** per formar un nou producte, el borilmetilsilà **3**. Altrament, quan s'utilitzen hidrocarburs litiats com el LiMe o el Li$^t$Bu, s'observa la formació d'altres productes. En el cas del LiMe, s'observa la formació del producte de la reacció $S_N2$ **4**, i en el cas del Li$^t$Bu, s'afavoreix la formació del producte de la reacció bor-Wittig **5**, sense arribar a formar-se el producte espiro-epoxi **6**.
4. S'ha estudiat la reacció entre la ciclohexanona i el compost **2**, on s'ha observat la formació del producte espiro-epoxi **6**, el qual ha sigut caracteritzat fent servir espectroscòpia RMN. A més a més, s'ha proposat un mecanisme per la formació del compost **6**.

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