

*“Organic chemistry just now is enough to drive one mad.  
It gives me the impression of a primeval forest full of the most  
remarkable things, a monstrous and boundless thicket, with no way  
of escape, into which one may well dread to enter.”*

**Friedrich Wöhler,**  
in a letter to Jacob Berzelius, January 28<sup>th</sup>, 1835.



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Even though this section marks the beginning of this manuscript, it is the last one I am typing, as I wanted my final lines to be dedicated to the many people involved in this work.

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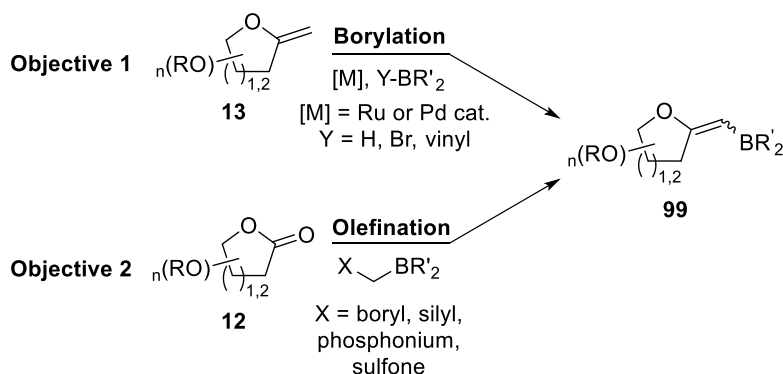
## Abstract

Glycals are unsaturated sugar derivatives constituting a large family of polyhydroxylated synthons. The *endo*-glycals are widely exploited as synthetic intermediates in the synthesis of natural products and as final molecules for biochemical applications. In contrast, the chemistry and bioactivity of *exo*-glycals remained unexplored until recently. However, their synthesis and use in biochemical applications is becoming the subject of increasing research interest. Their synthesis suffers nevertheless from some limitations regarding the substitution of the double bond. The control of the stereoselectivity is also a challenge.

Over the last decades, boron chemistry has witnessed major novel achievements and is now part of the standard toolbox of organic chemists. This is attributed to the accessibility and efficient conversion of the organoboron compounds into a wide array of diverse functional groups. Boron compounds have also stimulated the interest of the pharmaceutical industry for various applications, with several boron-containing drugs currently undergoing clinical trials.

Our work aims at the development of methods toward borylated *exo*-glycals which will be investigated as a platform to access a variety of polyfunctionalized *exo*-glycals as well as for their potential biochemical applications by our partners at UNamur.

Our synthetic strategy is based on two different approaches: the borylation of methylene *exo*-glycals **13** (**Objective 1**), and the olefination of readily available sugar lactones **12** using borylated reagents (**Objective 2**).



*General objectives of this work.*

For the first strategy, we experimented with the boryl-Heck coupling, the olefin metathesis, and the C-H activation method. Unfortunately, this work only resulted in the observation of side-reactions, non-reactivity, or degradation of our substrates.

We then turned our attention to the olefination of sugar lactones **12**. Four reactions were explored for this purpose: the boron-Wittig, the Peterson, the Wittig, and the modified Julia olefination reactions. The first two methods have been reported for the synthesis of borylated alkenes, but never applied to the glycals chemistry. In contrast, the latter two were successfully used to synthesize *exo*-glycals, but their borylating version was yet to be reported.

We started our investigations by considering the boron-Wittig reaction using *gem*-bisborylmethane. Despite our best effort, none of our reaction conditions or modified substrates afforded the desired borylated enol ether. We moved on to the *gem*-silylborylmethane-based Peterson olefination. Experimental and computational studies were carried out to deepen our understanding of these olefination processes, focusing especially on the boron-Wittig/Peterson chemoselectivity.

The exploration of a borylating version of the Wittig or modified Julia olefination required first the synthesis of suitable reagents. We synthesized two  $\alpha$ -boryl phosphonium salts and used them in the first formation of a vinylboronate *via* a Wittig reaction. However, the reagents proved unstable, and the yield was low. The synthesis of  $\alpha$ -boryl sulfones

was hindered by an autocondensation phenomenon. We adapted our synthetic pathway accordingly, but this work remains to be completed.



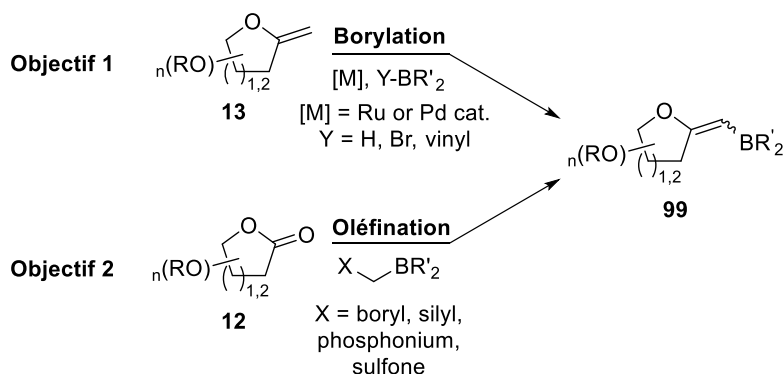
## Résumé

Les glycols sont des dérivés insaturés de sucres constituant une grande famille de synthons polyhydroxylés. Les *endo*-glycols sont largement exploités comme intermédiaires synthétiques dans la synthèse de produits naturels et comme molécules finales pour des applications biochimiques. En revanche, la chimie et la bioactivité des *exo*-glycols sont restées inexplorées jusqu'à récemment. Leur synthèse et leur utilisation dans des applications biochimiques suscitent cependant un intérêt croissant dans la recherche. Leur synthèse souffre néanmoins de certaines limitations concernant la substitution de la double liaison. Le contrôle de la stéréosélectivité de leur formation constitue également un défi.

Au cours des dernières décennies, la chimie du bore a connu des avancées majeures et fait désormais partie des outils standards des chimistes organiciens. Cela s'explique par l'accessibilité et la conversion efficace des composés organoborés en une large gamme de groupes fonctionnels divers. Les composés borés ont également stimulé l'intérêt de l'industrie pharmaceutique pour diverses applications, avec plusieurs médicaments contenant du bore actuellement en cours d'essais cliniques.

Notre travail vise à développer des méthodes pour la synthèse d'*exo*-glycols borylés, qui seront étudiés comme une plateforme permettant d'accéder à une variété d'*exo*-glycols polyfonctionnalisés ainsi que pour leurs potentielles applications biochimiques, en collaboration avec nos partenaires de l'UNamur.

Notre stratégie de synthèse repose sur deux approches distinctes: la borylation de méthylène *exo*-glycols **13** (**Objectif 1**) et l'oléfination de lactones de sucres **12** facilement accessibles en utilisant des réactifs borylés (**Objectif 2**).



*Objectifs généraux de ce travail.*

Pour la première stratégie, nous avons expérimenté le couplage boryl-Heck, la métathèse des oléfines et la méthode d'activation C-H. Malheureusement, ces tentatives ont seulement conduit à l'observation de réactions secondaires, d'absence de réactivité ou de dégradation de nos substrats.

Nous nous sommes ensuite tournés vers l'oléfination des lactones de sucres **12**. Quatre réactions ont été explorées à cet effet : les réactions de boron-Wittig, de Peterson, de Wittig et de Julia modifiée. Les deux premières méthodes ont été rapportées pour la synthèse d'alcènes borylés, mais jamais appliquées à la chimie des glycols. En revanche, les deux dernières ont été utilisées avec succès pour synthétiser des *exo*-glycols, mais leur version borylante n'a pas encore été rapportée.

Nous avons commencé nos investigations en considérant la réaction de boron-Wittig utilisant le *gem*-bisborylméthane. Malgré tous nos efforts, aucune de nos conditions réactionnelles ni les modifications des substrats n'ont permis d'obtenir l'éther d'énol borylé souhaité. Nous sommes ensuite passés à l'oléfination de Peterson basée sur le *gem*-silylborylméthane. Des études expérimentales et computationnelles ont été menées afin d'approfondir notre compréhension de ces processus d'oléfination, en particulier de la chimiosélectivité boron-Wittig/Peterson.

L'exploration d'une version borylante des réactions de Wittig ou de Julia modifiée a d'abord nécessité la synthèse de réactifs appropriés. Nous avons synthétisé deux sels de phosphonium  $\alpha$ -borylés et les avons utilisés



pour la première formation d'un vinyle boronate *via* une réaction de Wittig. Cependant, les réactifs se sont révélés instables, et le rendement obtenu était faible. La synthèse de sulfones  $\alpha$ -borylées a été entravée par un phénomène d'autocondensation. Nous avons adapté notre voie synthétique en conséquence, mais les travaux restent à finaliser.



## Abbreviations

|                                                           |                                            |
|-----------------------------------------------------------|--------------------------------------------|
| 12-crown-4: 1,4,7,10-Tetraoxacyclododecane                | DG: directing group                        |
| <sup>13</sup> C NMR: Carbon-13 nuclear magnetic resonance | dtbpy: 4,4'-Di-tert-butyl-2,2'-dipyridyl   |
| <sup>1</sup> H NMR: Proton nuclear magnetic resonance     | E: electrophile                            |
| 9-BBn: 9-borabicyclo(3.3.1)nonane                         | EDG: Electron donating group               |
| Ac: acetyl                                                | EE: ethoxyethyl                            |
| Acac: acetylacetone                                       | eq.: equivalents                           |
| BrBcat: 2-Br-1,3,2-benzodioxaborole                       | Et <sub>2</sub> O: diethylether            |
| BHT: butylated hydroxytoluene                             | EWG: Electron withdrawing group            |
| Bn: benzyl                                                | GlT: galactofuranosyltransferase           |
| ca.: circa                                                | Het: heteroaryl                            |
| cat: catecholato                                          | HMDS: hexamethyldisilazane                 |
| Cb: <i>N,N</i> -diisopropylcarbamoyl                      | HMPA: Hexamethylphosphoramide              |
| COD: Cycloocta-1,5-diene                                  | HRMS: High resolution mass spectroscopy    |
| Cp: cyclopentadienyl                                      | <i>i</i> : iso                             |
| Cy: cyclohexyl                                            | IDCT: Iodonium sym-dicollidine perchlorate |
| DABCO: 1,4-diazabicyclo[2.2.2]octane                      | L.A.: Lewis acid                           |
| DAN: diaminonaphtalene                                    | LDA: lithium diisopropylamine              |
| dba: dibenzylideneacetone                                 | LiTMP: Lithium tetramethylpiperidide       |
| DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene                   | MDAN: dimethyldiaminonaphtalene            |
| DCM: dichloromethane                                      | MDEA: <i>N</i> -methyldiethanolamine       |
|                                                           | Mes: mesityl                               |

|                                                             |                                                |
|-------------------------------------------------------------|------------------------------------------------|
| MIDA: <i>N</i> -methyliminodiacetic acid                    | rf: retention factor                           |
| MMPP: magnesium monoperoxyphthalate                         | RT: Room temperature                           |
| MOF: metal organic framework                                | <i>t</i> : tert                                |
| MOP: methoxypropyl                                          | TES: triethylsilyl                             |
| Ms: mesyl group                                             | Tf: triflic                                    |
| MS: molecular sieve                                         | TFA: trifluoroacetic acid                      |
| MW: microwave                                               | TFAA: trifluoroacetic acid anhydride           |
| <i>n</i> : normal                                           | THF: tetrahydrofuran                           |
| napht: naphthyl                                             | TLC: thin-layer chromatography                 |
| NFSI: <i>N</i> -fluorobenzenesulfonimide                    | TMEDA: Tetramethylethylenediamine              |
| NHC: <i>N</i> -heterocyclic carbene                         | TMP: 2,2,6,6-tetramethylpiperidide             |
| Nu: nucleophile                                             | TMS: trimethylsilyl                            |
| pin: pinacolato                                             | TMTAN: 1,4,7-Trimethyl-1,4,7-triazacyclononane |
| PMDTA: <i>N,N,N',N'',N''</i> -pentamethyldiethylenetriamine | tol: tolyl                                     |
| <i>p</i> TSA : <i>p</i> -toluenesulfonic acid               | TS: Transition state                           |
| quant.: quantitative yield                                  | UMP: uridinemonophosphate                      |

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| Triphenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phosphonium iodide ( <b>300</b> ) .....        | 251 |
| Triphenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phosphonium bromide ( <b>302</b> ) .....       | 252 |
| (Iodomethyl)boronic acid ( <b>305</b> ) .....                                                                | 253 |
| (Bromomethyl)boronic acid ( <b>306</b> ) .....                                                               | 254 |
| Potassium (iodomethyl)trifluoroborate ( <b>309</b> ) .....                                                   | 255 |
| Potassium (bromomethyl)trifluoroborate ( <b>308</b> ) .....                                                  | 256 |
| Tris(phenyl)methylphosphonium triflate ( <b>314</b> ) .....                                                  | 257 |
| 2-(methylsulfonyl)benzo[d]thiazole ( <b>321</b> ) .....                                                      | 258 |
| 5-(methylsulfonyl)-1-phenyl-1 <i>H</i> -tetrazole ( <b>324</b> ) .....                                       | 259 |
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## 1. Introduction

### 1.1. The glycal family

Sugar chemistry, or carbohydrate chemistry, is a crucial field in both chemical and biological sciences due to its broad applications and fundamental significance. Indeed, carbohydrates are among the most abundant and essential biomolecules, playing vital roles in various biological processes. Accordingly, sugar chemistry is a cornerstone of both fundamental research and practical applications across various fields, from medicine to materials science, making it an indispensable area of study.<sup>[1]</sup> Modifications of the carbohydrate structure give rise to a diverse subfamily of molecules, each with unique structures and functions derived from carbohydrates.

One such derivative is the glycal family, characterized by a carbon-carbon double bond located at the anomeric position. Their first discovery and synthesis resulted from the work of Fischer (1902 Nobel laureate) and Zach in 1913.<sup>[2]</sup> They were mistakenly convinced that the insaturation they obtained was an aldehyde function, and the name “glycal” was coined accordingly.<sup>[3]</sup> While glycal is a general name, specific derivatives, derived from glucose for instance, are commonly called glucals, while the ones that originate from galactose are referred to as galactals. Depending on the monosaccharide used as a starting material, glycals can be formed as pyranose (six-membered) or furanose (five-membered) rings. Another important subdivision is made regarding the nature of the double bond. In *endo*-glycals, the double bond is located within the ring structure of the sugar molecule (**Figure 1**, left). On the other hand, *exo*-glycals are characterized by a carbon-carbon double bond that extends outside the ring structure (**Figure 1**, right).

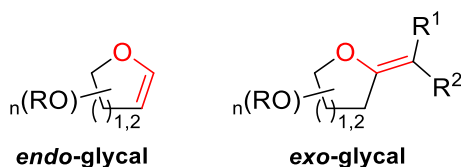
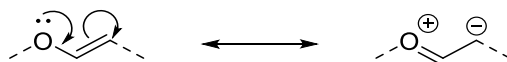


**Figure 1:** glycal subdivision

While many divergences can be pointed out between *endo*- and *exo*-glycals, both of them see their reactivity dictated by their enol ether component (**Figure 1**, in red). This function is defined as an alkoxy-substituted alkene. This specific atom sequence allows for an extended pi-system compare to simple alkenes (**Scheme 1**). Enol ethers are versatile intermediates in organic chemistry due to their electron-rich double bond, which makes them reactive towards electrophilic addition, cycloaddition, and metal-catalyzed reactions. Their unique reactivity allows for the construction of a wide variety of complex molecules, making them valuable tools in synthetic chemistry.<sup>[4]</sup>



**Scheme 1:** general reactivity of enol ethers

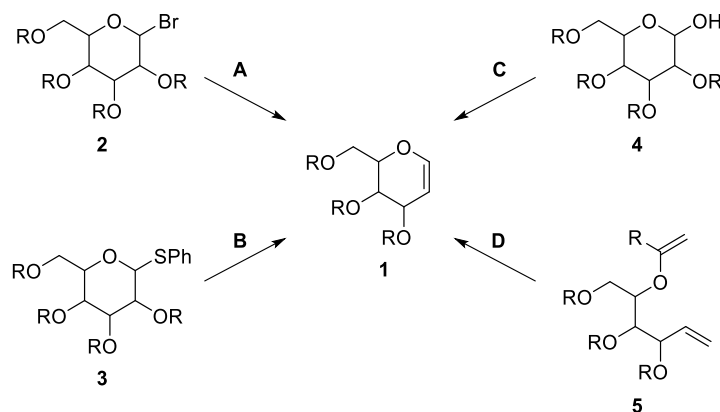
#### 1.1.1. *Endo*-glycals

Synthesized for the first time over a century ago, *endo*-glycals were for a long time the only known type of glycal.<sup>[2]</sup> They have many uses in synthetic carbohydrate chemistry, directly or indirectly related to glycosylation, owing to their highly reactive double bond (see **Scheme 3**). They constitute a useful tool for exploring carbohydrate scaffolds in drug discovery, due to the growing interest for the development of new glycomimetic medical therapeutics. They also found a purpose as a probe for the study of biological process, notably enzymatic ones.

Until this day, the *endo*-glycals still attract the major part of the glycal attention, to the point that some scientific papers simply refer to them as “glycal”, omitting the regiochemistry prefix in a misuse of the name. As a result of this focused interest, the chemistry of *endo*-glycals has been extensively explored, covering both synthetic methods and applications.

Fischer and Zach original synthesis was based on the reductive elimination of an acetylated glycosyl bromide using zinc and acetic acid.<sup>[2]</sup> The acidic nature of the medium typically leads to the formation of several cyclic and open side products, including the isomer resulting from the allylic rearrangement of the glycal **1**. Since then, multiple variations of that

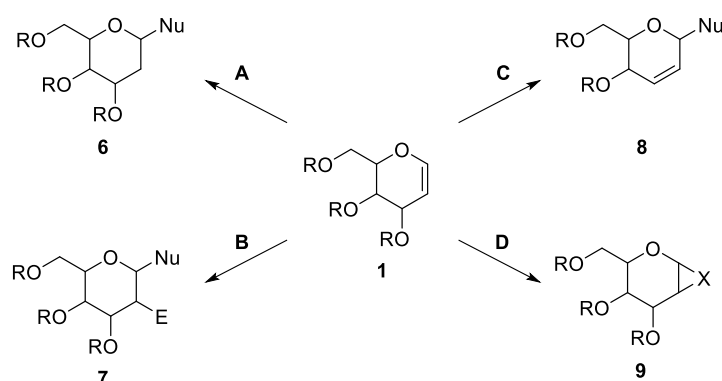
strategy were developed, using reducing agents such as Zn or SmI<sub>2</sub> at neutral pH to perform a reductive elimination of protected bromide derivatives **2** (**Scheme 2, A**).<sup>[5]</sup> A further evolution of that process uses lithium or sodium and naphthalene to react with thioglycosides **3** (**Scheme 2, B**).<sup>[6]</sup> Another strategy based on a combination of deoxygenation (typically, a Barton-McCombie reaction) and dehydration is used to yield the desired glycal starting from protected sugar **4** (**Scheme 2, C**).<sup>[7]</sup> It is also noteworthy that *endo*-glycals can be made from acyclic starting materials such as **5** through a ring closing metathesis strategy exploiting a molybdenum-based Schrock catalyst (**Scheme 2, D**).<sup>[8]</sup>



**Scheme 2:** overview of the synthetic pathways toward *endo*-glycal

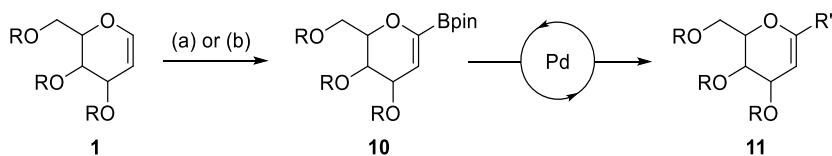
The interest for glycal chemistry is attributed to their ability to be easily transformed into various derivatives, as depicted in **Scheme 3**.<sup>[9]</sup> This reactivity turned the *endo*-glycals into highly valuable synthons for the synthesis of *c*-glycoside natural products.<sup>[10]</sup> The reaction with a nucleophile type NuH leads to 2-deoxy glycosides **6** (**Scheme 3, A**).<sup>[11]</sup> This pattern is found in multiple natural products, where the absence of the hydroxy group governs the biological activity. Reaction with NuE generates more functionalized glycosides **7** (**Scheme 3, B**).<sup>[12]</sup> Another common transformation of *endo*-glycal is the Ferrier rearrangement in which, under the influence of a Lewis acid, a nucleophilic substitution at the anomeric position is accompanied by an allylic shift to obtained **8** (**Scheme 3, C**).<sup>[13]</sup> This reaction can be facilitated when the RO leaving group is pseudo-axial, which promotes a vinylogous anomeric effect ( $n_{\text{O}}-\pi_{\text{C}=\text{C}} \rightarrow \sigma^*_{\text{C}-\text{O}}$ ).

interaction).<sup>[14]</sup> This strategy has found numerous applications in the field of natural product synthesis.<sup>[15]</sup> The reactive carbon-carbon double bond also allows for the formation of bicyclic compound **9** through an epoxidation (**Scheme 3, D**, X = O) or a cyclopropanation (**Scheme 3, D**, X = CR<sub>2</sub>).<sup>[6, 15]</sup> These reactive three-membered rings serve as a platform to reach more complex structures.



**Scheme 3:** some key synthetic transformations from *endo*-glycal

Notable progress has also been made in constructing C1-substituted glycals through transition metal-catalyzed Stille, Negishi, Hiyama-Denmark and Heck cross-coupling reactions.<sup>[17]</sup> Among them, the environmentally friendly Suzuki–Miyaura cross-coupling reaction stands out as a crucial tool in glycal-based cross-coupling. Such carbon-carbon bond formations would classically be carried out from electrophilic glycals, substituted with a halogen, a sulfone or a phosphonate group at the anomeric position, and a borylated partner. Unfortunately, these electrophilic *endo*-glycals are unstable.<sup>[18]</sup> An alternative version was consequently developed, where a nucleophilic *endo*-glycal **10** carrying a boronate group reacts with various electrophiles (**Scheme 4**).



(a)  $B_2pin_2$ ,  $Ir(OMe)(COD)$ ,  $dtbpy$ , octane,  $80^\circ C$ , 16h. (b)  $tBuLi$ ,  $B(OMe)_3$ ,  $-78^\circ C$ , toluene, then pinacol.

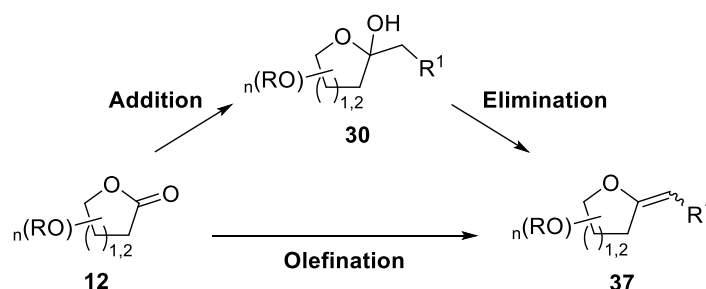
**Scheme 4:** borylated *endo*-glycals as Suzuki-Miyaura coupling partners

Borylated *endo*-glycals **10** can be obtained by two methods. The iridium-catalyzed borylation of glycals **1** occurs under relatively mild conditions with good yields and excellent regioselectivity (**Scheme 4, a**).<sup>[19]</sup> The Bpin derivatives being often difficult to purify, other boronate groups were considered for the coupling reaction. While the iridium strategy tolerates various protecting groups and would be suitable for late stage functionalization, the modification the boronate moiety would require the use of different bisboryl reagents, not readily accessible. The deprotonation pathway developed by Parkan *et al.* requires harsher conditions, but the nature of the boron group can be easily tuned by using the corresponding alcohol (**Scheme 4, b**).<sup>[20]</sup> Further upgrade of this method was reported by the same research team using ether protecting group EE and MOP, allowing for an affordable and scalable chemistry.<sup>[21]</sup> The Suzuki-Miyaura cross-coupling methodology enables the efficient assembly of  $Csp^2$ - $Csp$ ,  $Csp^2$ - $Csp^2$ , and  $Csp^2$ - $Csp^3$  bonds in good to excellent yields under mild reaction conditions.<sup>[22]</sup>

#### 1.1.2. *Exo*-glycals

Unlike its *endo* counterpart, the *exo*-glycal chemistry is a relatively recent topic. The first synthesis of an *exo*-glycal was reported by Bischofberger in 1975, who studied the reaction of ethyl isocyanoacetate with lactones, almost sixty years after Fischer and Zach's work.<sup>[23]</sup> In the next decade, the studies led by Chapleur<sup>[24]</sup> and Wilcox<sup>[25]</sup> offered the first reliable synthetic methods and kick-started the study of that family of compound. These early reports perfectly illustrate the two main pathways used to access *exo*-glycals (**Scheme 5**). The first one involves the direct formation of an anomeric double bond through an olefination process,

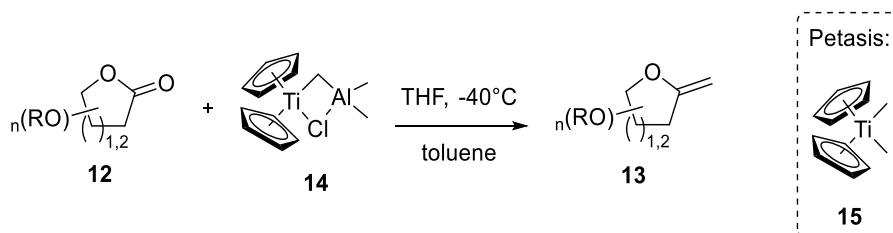
typically starting from a carbonyl group. In this regard, lactones are ideal, readily available starting compounds. The second method is a stepwise process based on the creation of a carbon-carbon bond at the anomeric center, followed by the formation of a double bond via an elimination reaction. Here again, sugar lactones **12** are evident but not exclusive substrates. The most used synthetic routes will be illustrated hereafter.



**Scheme 5:** General pathways from sugar lactones to *exo*-glycals.

#### 1.1.2.1. Synthesis of *exo*-glycals

The simplest *exo*-glycal is the unsubstituted methylene derivative **13**. Using Tebbe's **14** or Petasis' reagents **15**, both titanocene-based methylene transfer agents, furano- and pyranoglycals carrying a terminal double bond can be formed (**Scheme 6**).<sup>[26-27]</sup> While the Petasis reagent has the advantage of being aluminium free and more conveniently prepared, it also requires higher temperatures to be activated.<sup>[28]</sup> The terminal carbon-carbon double bond of those *exo*-glycals is fairly reactive, making them a suitable platform for further functionalization.

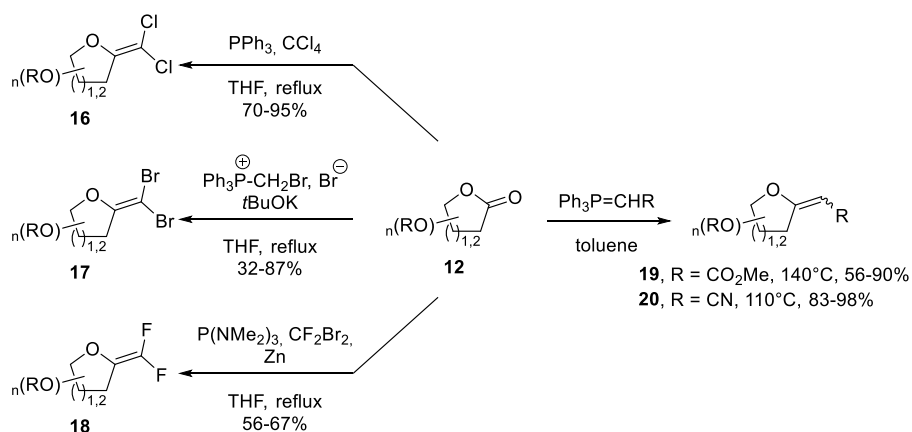


**Scheme 6:** Synthesis of the first methylene *exo*-glycal<sup>[25]</sup>

Early on, Wittig reactions and similar processes dubbed “Wittig-like” reactions were used to transform sugar lactones **12** (**Scheme 7**). The



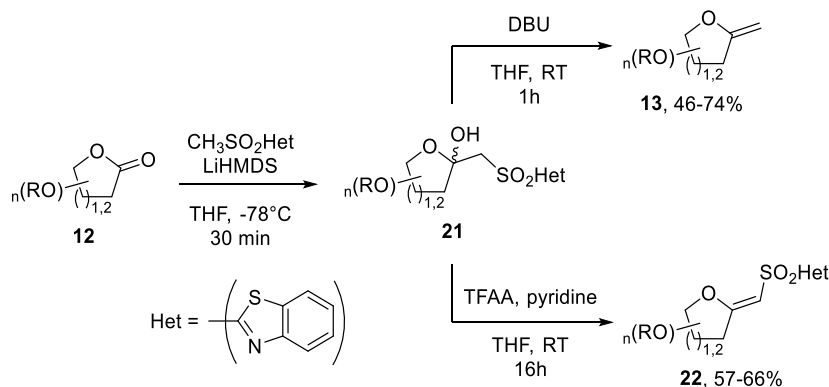
initial work by Chapleur used tetrachloromethane and tris(dimethylamino)phosphine to generate  $\text{CCl}_3^-$ , as in an Appel reaction. This carbanion then served as the nucleophile to obtain dichloro derivatives **16**.<sup>[24]</sup> Limited to 1,4-lactones protected with an acetonide group, the conditions were tweaked and triphenylphosphine was used to broaden the scope. In an attempt to form monobromo *exo*-glycals, Chapleur *et al.* used a brominated phosphonium salt and a *tert*butoxy base.<sup>[29]</sup> They serendipitously observed the generation of the dibromo derivative **17**. Difluoro substituted *exo*-glycals **18** were also synthesized by the group of Motherwell using tris(dimethylamino)phosphine and dibromodifluoromethane activated with zinc.<sup>[30]</sup> Wittig reactions are also capable to create new carbon-carbon double bond, although this method is limited to stabilized phosphonium ylides. Double bond carrying an ester group **19** or a cyano group **20** were obtained in good yield, but the process requires a high temperature and sealed vessels.<sup>[31]</sup> No significant *Z/E* selectivity were observed in these transformations.



**Scheme 7:** Wittig-like reactions applied to sugar lactones

More recently, Gueyrard *et al.* exploited the modified Julia olefination to prepare methylene *exo*-glycals (**Scheme 8**). Deprotonated methylbenzothiazoylsulfone reacts with sugar lactone to reach  $\alpha$ -heteroarylsulfone hemiketal intermediate **21**. The subsequent Smile rearrangement can be triggered by DBU to obtain the anomeric methylene derivative **13** in moderate yields.<sup>[32]</sup> Various lactones and protecting groups were tolerated by this method. Interestingly, a dehydration of the same

intermediate **21** can be achieved by forming and eliminating a trifluoroacetate. As a result, the C-glucosyl vinyl sulfones **22** were obtained in reasonable yield with exclusive Z-selectivity.<sup>[33]</sup>

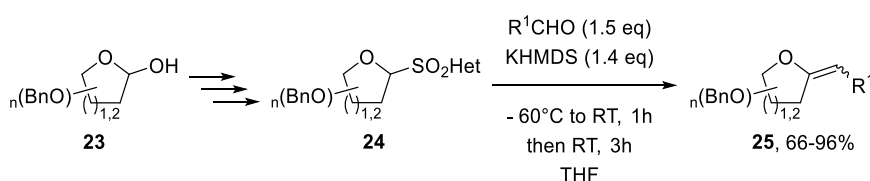


**Scheme 8:** Gueyrard's early work on modified Julia olefination.

To continue their work, the same group developed a method for the synthesis of alkylated tri- and tetrasubstituted *exo*-glycals.<sup>[34]</sup> Built on the DBU strategy, suitable Julia reagents led to the formation of double bonds carrying methyl, dimethyl, hexyl, cyclopentylidene or allyl group, in moderate to good yield. Both pyranose and furanose rings were efficiently transformed with the *E* *exo*-glycal as the major isomer. This methodology was further exploited to synthesize fluorinated C-glycosylidenes. Twenty-three monofluorinated compounds, tri- or tetrasubstituted, were obtained using DBU and the appropriated Julia reagent.<sup>[35]</sup> Various sugar structures and protecting groups were compatible with the procedure, with reported yields going from 37% to 94%. Depending on the nature of the sugar, the observed stereoselectivity oscillated between 5:95 *E/Z* and 80:20 *E/Z*. Difluorinated compounds were also obtained, although some more optimization was required. Indeed, the DBU mediated rearrangement did not take place. Instead, a thermal activation in the absence of a base proved effective. Most of the tested substrates were converted efficiently at  $140^\circ\text{C}$ , under microwave irradiations, with the notable exception of silyl-protected sugars.<sup>[36]</sup>

A significant alteration of this modified Julia procedure was reported by Oka *et al.* They swapped the carbonyl and sulfone functions

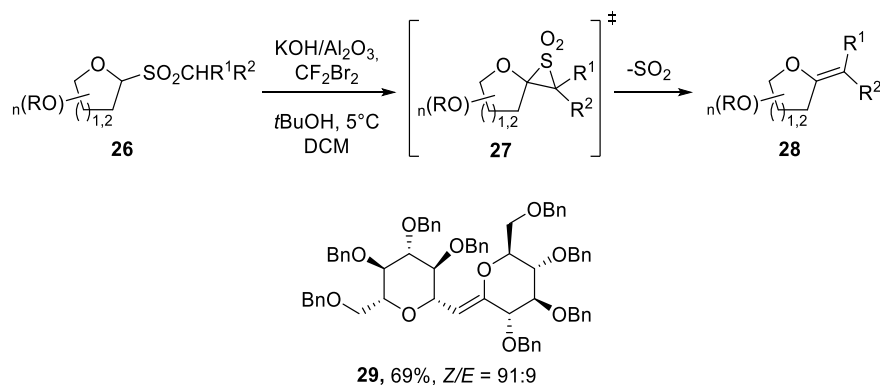
between the starting materials, using 1,2-*cis*-glycosyl sulfones **24** with aldehydes.<sup>[37]</sup> The sulfones are obtained in three steps from benzyl-protected sugars **23**. The free alcohol is transformed into a more nucleofugic trimethylsilylether. Using TMSI, the iodide derivative is generated *in situ* to facilitate the nucleophilic attack of a Het-SH thiol. The resulting sulfide is then oxidized using magnesium monoperoxyphthalate (MMPP). The olefination occurs upon deprotonation of the sulfone **24** and reaction with an aldehyde (**Scheme 9**). The reported substrates consist of furanoses and glucopyranoses, with good to excellent yields. Substitution pattern of the formed *exo*-glycals **25** includes electron-rich or poor aryl, styryl and cyclohexyl groups and *E/Z* ratio going from 43:57 to 91:9. This version of the modified Julia olefination benefits from the use of readily available lactones, at the cost of the preliminary formation of glycosyl sulfones. These three synthetic steps are however well studied. Notably, 1,2-elimination of glycosylsulfones produces *endo*-glycals.<sup>[38]</sup> They are also the backbone of the *exo*-glycals synthesis by the Ramberg-Bäcklund rearrangement (vide infra).<sup>[39]</sup>



**Scheme 9:** Oka's version of the Julia olefination.

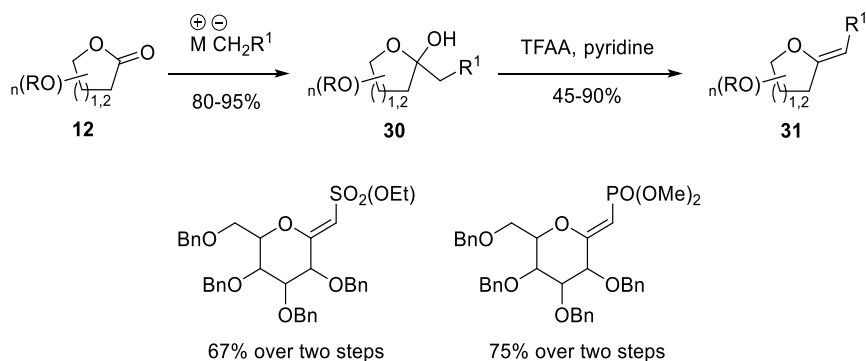
The Ramberg-Bäcklund procedure for preparing *exo*-glycals from carbohydrate-derived sulfones **26** was developed simultaneously and independently by the groups of Taylor and Franck.<sup>[40]</sup> The rearrangement necessitates the installation of a halogen in  $\alpha$  position of the sulfone to act as a leaving group. This can be achieved *in situ* with  $\text{CCl}_4$  in the presence of KOH, as described by Meyers.<sup>[41]</sup> A further modification of the conditions, using  $\text{CF}_2\text{Br}_2$ , evidently improved the yield.<sup>[42]</sup> The anomeric position is then deprotonated, leading to the formation of an unstable episulfone **27** that decomposes with extrusion of sulfur dioxide (**Scheme 10**). Various terminal ( $\text{R}^1 = \text{R}^2 = \text{H}$ ), monosubstituted ( $\text{R}^1 = \text{Ph, Me, Et; R}^2 = \text{H}$ ) and disubstituted ( $\text{R}^1 = \text{R}^2 = \text{Me, Ph, cyclohexyl, adamantyl}$ ) double bonds **28** were thus formed. The Ramberg-Bäcklund rearrangement was also put to use to reach more

complex *exo*-glycals such as **29**. Upon reduction of the double bond (*vide infra*), such compounds give rise to C-linked disaccharides.<sup>[43]</sup>



**Scheme 10:** Ramberg-Bäcklund rearrangement applied to *exo*-glycals synthesis.

Lastly, an efficient strategy based on an addition-elimination sequence was used by several groups to obtain *exo*-glycals of biological significance. An organolithium or an organomagnesium performs a nucleophilic attack on protected sugar lactones **12**. The alcohol formed **30** is then converted into a suitable leaving group to undergo elimination in a subsequent step (**Scheme 11**).<sup>[44]</sup> Since the initial work by Lin *et al*, this method was applied to the synthesis of monosubstituted *exo*-glycals **31** bearing allyl, phenyl, phosphonyl and sulfonyl groups in good to excellent yield.<sup>[45]</sup> Interestingly, only the *Z* olefin is formed, pointing to the existence of an oxonium intermediate during the elimination step.<sup>[46]</sup>



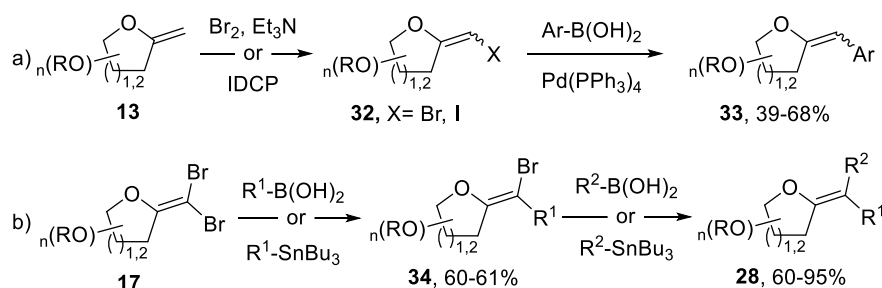
**Scheme 11:** Addition-elimination sequence from sugar lactones.

While several methods have been established for the synthesis of *exo*-glycals, most of them are hindered by a very narrow scope. Notably, very few strategies can afford enol ethers bearing electron withdrawing groups. Also, controlling the stereoselectivity of the newly constructed double bond remains a challenge.

#### 1.1.2.2. Synthetic uses of *exo*-glycals

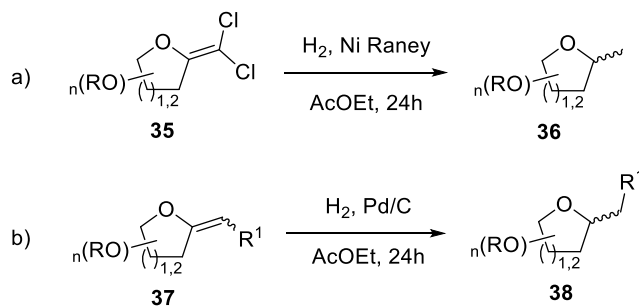
Although C-glycoside formation from *exo*-glycals is probably one of the first motivations to investigate the chemistry of these compounds, many other transformations have been studied, owing to the high reactivity of the glycal C-C double bond. As an overview, cross-coupling C-C formation, C-H formation by reduction, and connection of heteroatoms will be illustrated.

López *et al.* were the first to functionalize *exo*-glycals using cross-coupling strategies, thereby expanding this family of molecules. Halogenated *exo*-glycals **32**, synthesized from 1-*exo*-methylenes **13**, reacted with aryl boronic acids in presence of tetrakis(triphenylphosphine)palladium to give the arylated *exo*-glycals **33** (**Scheme 12**, a). Yields were moderate to good according to the nature of protecting groups and boronic acids.<sup>[47]</sup> Products were obtained as a unique isomer of unknown configuration. The same group continued their work with the successful development of the Sonogashira and Stille coupling reactions. An advanced application of the cross-coupling of *exo*-glycals was reported by Chapleur *et al.* Starting from the dibromo derivatives **17**, they were able to sequentially and selectively replace each bromine atoms (**Scheme 12**, b).<sup>[48]</sup> The Stille and Suzuki coupling proved equally effective, and both methods yielded the monobrominated product **34** in good yield, with the *Z* isomer as major products. The second coupling led to tetrasubstituted olefin **28** in good to excellent yields.



**Scheme 12:** Examples of cross-couplings carried out on *exo*-glycals.

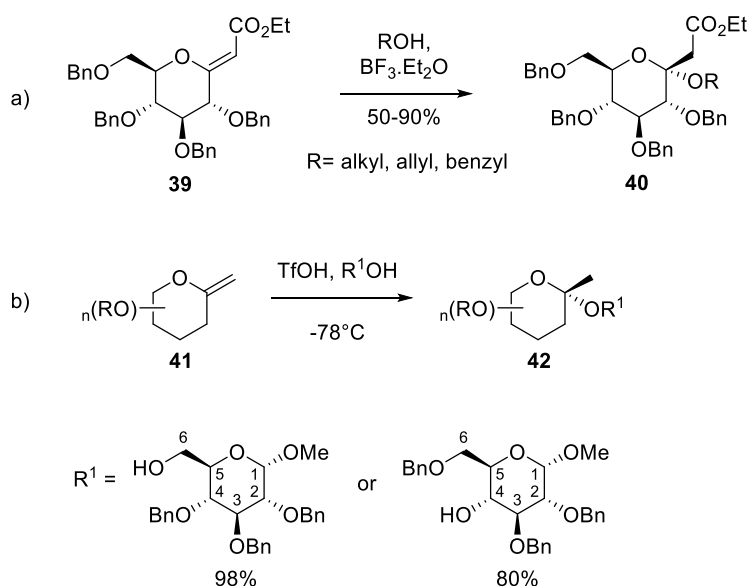
The simple reduction of the double bond of *exo*-glycals has been largely investigated. Indeed, the introduction of a methyl group at the anomeric position in a stereocontrolled manner is not a straightforward operation. While the reduction of methylene derivatives **13** was reported,<sup>[25-26]</sup> a better regulation of stereochemistry of the anomeric position was attained starting from dichloro *exo*-glycals **35**.<sup>[49]</sup> Using Raney nickel, both the reduction and the dehalogenation proceeded smoothly (**Scheme 13**, a). The hydrogen atoms adsorbed on the surface of the catalyst will add to the less hindered face of the double bond. The methylated compounds **36** were obtained in good to excellent yields, with a high control of the newly formed stereocenter. Substituted *exo*-glycals **37** were successfully reduced under hydrogen atmosphere using palladium catalyst (**Scheme 13**, b).<sup>[50]</sup>



**Scheme 13:** Reduction of *exo*-glycals using (a) Ni Raney or (b) Pd/C.

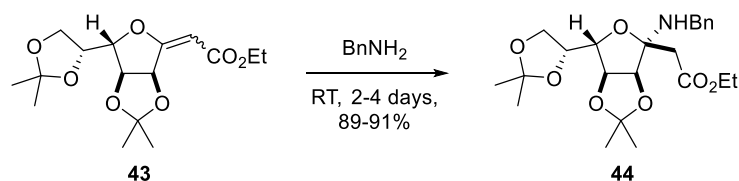
Ketoside compounds are accessible through *exo*-glycals functionalization. Lin *et al.* reported a preliminary study on alcohol addition to activated olefin **39**. Upon treatment with alcohol in the presence of a

Lewis acid,  $\alpha$  glycosides **40** were obtained in generally good yield (**Scheme 14, a**).<sup>[51]</sup> When a sugar is used in lieu of the alcohol, *exo*-glycals offer a unique way to build complex disaccharides. Ikegami's group has investigated this area, starting from benzyl or acetyl protected *exo*-methylene derivatives **41** (**Scheme 14, b**). Almost quantitative yields of disaccharides **42** were obtained with sugars unprotected at position 6 or 4 upon triflic acid activation. These reactions have been performed using *exo*-glycals of gluco, manno, and galacto configuration and  $\alpha$  anomers were formed in all cases.<sup>[52]</sup>



**Scheme 14:** Formation of C-O bond on *exo*-glycals.

C-N bond can be constructed from activated *exo*-glycals **43** acting as Michael acceptors. After a few days in benzylamine, adducts **44** were obtained in excellent yields. The benzylamino group was found to be in a trans relationship with the protecting dioxolane rings. (**Scheme 15**). Therefore, it is postulated the amine is approaching on the less hindered face. The products formed consist of a next class of  $\beta$ -amino acids. Hydrogenolysis of the benzyl group opens possibilities towards peptide chemistry.<sup>[53]</sup>



**Scheme 15:** C-N bond formation through benzylamine addition.

#### 1.1.2.3. Biological applications of *exo*-glycals

Besides their synthetic interest, *exo*-glycals have been exploited for the inhibition of biologically relevant enzymes. Natural occurrences of *exo*-glycal-containing molecules were recently reported, like the bombyxamycin B **45** that showed mild antibacterial and antiproliferative effects (**Figure 2**).<sup>[54]</sup> The biological activities of synthetic *exo*-glycals were also studied. Diphosphonate compound **46** was obtained through a formal addition-elimination procedure, and exhibits anticancer properties. It acts as a sialyltransferase inhibitor, with an affinity for the enzyme thousand times greater than the natural substrate.<sup>[55]</sup> Vincent *et al.* targeted the galactofuranosyltransferases (GlfT) vital for *Mycobacterium tuberculosis*. Compound **47** was obtained with a combination of addition-elimination to obtain the phosphonylated *exo*-glycal, followed by a Selectfluor fluorination. This glycal was demonstrated to be a competitive inhibitor of both GlfT 1 and GlfT 2.<sup>[56]</sup> Gueyrard *et al.* took advantage of the recent development in the modified Julia olefination to synthesize potential glycosidase inhibitors. Glycosidases represent interesting targets for numerous diseases such as viral infections, diabetes and cancers. Compound **48** was found to be a potent and selective inhibitor of  $\beta$ -glucosidase.<sup>[57]</sup>



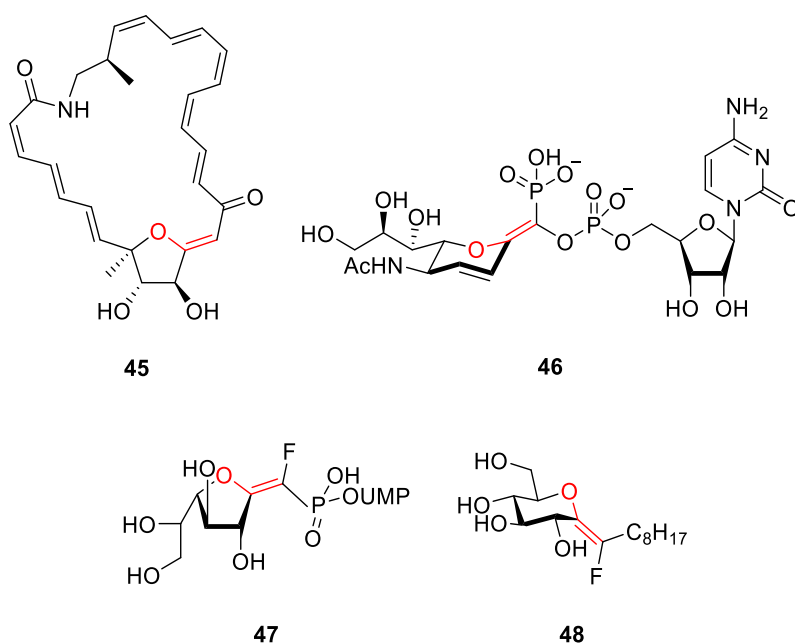


**Figure 2:** Biologically active *exo*-glycals.

One can notice that each of these compounds are carrying an electron withdrawing group on the double bond, creating a push-pull effect. This can be rationalized by comparison between the putative transition state of the natural substrate and their synthetic inhibitors counterparts (**Figure 3**). The interaction with the enzymatic cavity promotes the oxonium form, with a negative charge developing in  $\alpha$  to the electron withdrawing group.<sup>[58]</sup> While phosphonyl, sulfonyl, ester and fluorine groups were explored in this regard, no example of borylated *exo*-glycal was reported. Nonetheless, boryl moieties are biocompatible and could act as a negative charge stabilizers.

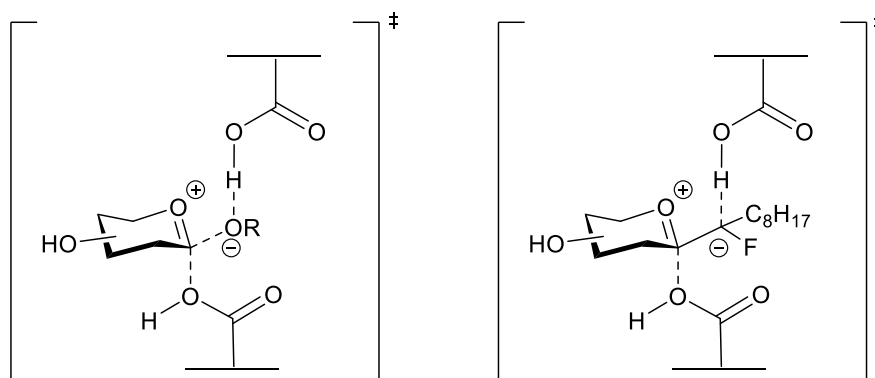


**Figure 3:** Transition state of the glycosidase and its guest. Left: the natural substrate, right: the synthetic inhibitor.

## 1.2. The organoboron chemistry

### 1.2.1. Attractiveness of the boron properties

Organoboron compounds are versatile intermediates and as such are some of the most important classes of reagents in modern organic chemistry. This stems from their ease of preparation combined with their ability to undergo a broad range of chemical transformations.<sup>[59]</sup> Notably, boron chemistry has involved two Nobel prizes to Brown (1979, with Wittig) and Suzuki (2010, with Heck and Negishi) for the application of boron compounds in organic synthesis. The relative reactivity of the C-B bond and the Lewis acidity of the boron are the main attractive features of this chemistry. Classification of boron compounds has been well established, from boranes (containing only B-H or B-C bonds) to borates (featuring only B-O bonds) (**Figure 4**).

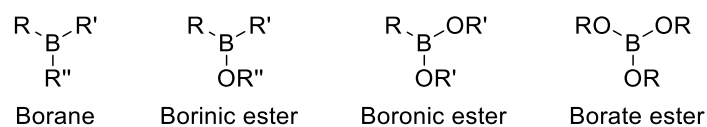
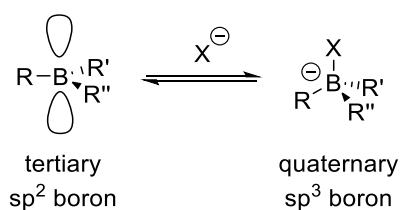


**Figure 4:** Nomenclature of the most common boron compounds.

The boron atom of these compounds is  $sp^2$  hybridized, featuring an empty p orbital perpendicular to the substituents, in a trigonal planar geometry (**Scheme 16**). This empty orbital is the source of the Lewis acidity

of the boron. Indeed, this tertiary structure can create a quaternary boron center upon complexation with a Lewis base. To accommodate four substituents, the boron adopts a  $sp^3$  hybridization, along with a tetragonal geometry. Since the empty p orbital is no longer present and the Lewis acidity is quenched, these negatively charged ate-complexes are nucleophilic, a property exploited in a plethora of transformations (*vide infra*).



**Scheme 16:** Equilibrium of the tertiary and quaternary forms of boron.

There are two naturally occurring NMR active nuclei of boron,  $^{11}\text{B}$  (80.1%) and  $^{10}\text{B}$  (19.9%). Owing to their nuclear spin of 3/2 and 3 respectively, both isotopes are the source of quadrupolar effect. With its higher natural abundance, higher gyromagnetic ratio, and lower quadrupole moment,  $^{11}\text{B}$  is the better suited nucleus to use in NMR. Interestingly, the signal's shift is a direct indication of the boron atom's surrounding. Boranes  $\text{R}_3\text{B}$  can be found around 90~80 ppm, but a higher electron density on the boron center results in  $^{11}\text{B}$  resonance at higher fields, with boronic esters' shift at 30 ppm and the quaternary  $\text{R}_4\text{B}^-$  lying at -20 ppm.

The last three decades have witnessed the evolution of boronic esters from ordinary organoelement compounds to powerhouses in organic and organometallic chemistry and catalysis.<sup>[60]</sup> The seemingly never-ending interest in these types of compounds appears to be fueled by the high efficiency and broad applicability of the Suzuki-Miyaura coupling, specifically in the synthesis of pharmaceutical and agrochemical intermediates and natural products.<sup>[61]</sup> Various boronic ester groups have been developed along the years (**Figure 5**). Catechol (Bcat) **49** and pinacol (Bpin) **50** are the more prevalent ligands, but chiral groups can also be used such as the pinanediol **51**. The notion of boronic ester is expended to boronamide compounds, with diaminonaphtalene (BDAN) **52** being the

most used. N-methyliminodiacetic acid (BMIDA) **53** has also received attention as a robust boron group, the lone electron pair of the nitrogen being ideally located to coordinate the empty p orbital of the boron. Trifluoroboronate compounds **54** display the same reactivity as boronic esters toward Suzuki-Miyaura coupling, despite its quaternary boron center.<sup>[62]</sup>

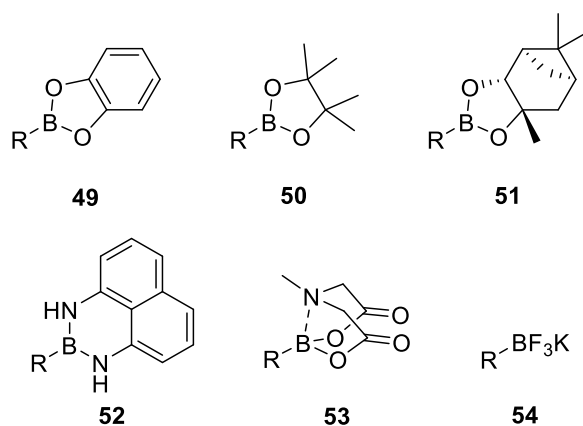
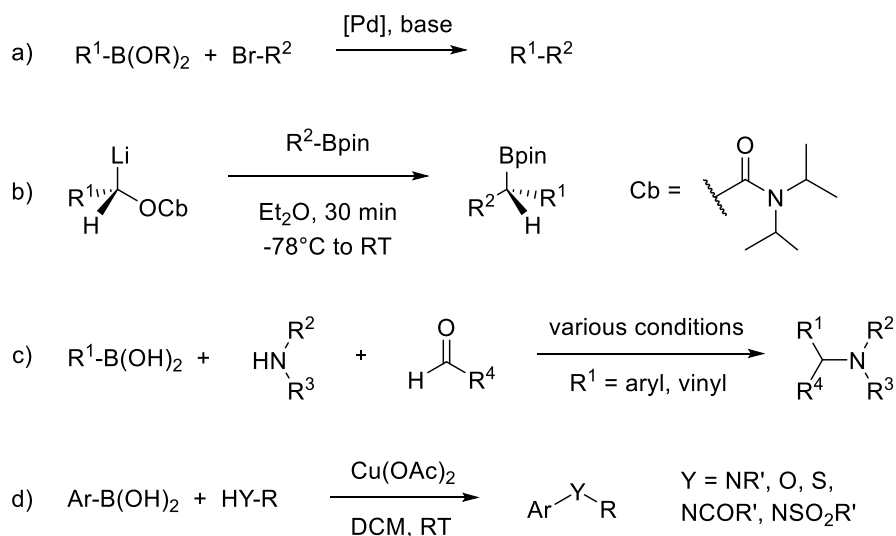


**Figure 5:** Widely spread boronic ester groups.

Owing to those properties, reactions involving boron atoms play a crucial role in modern synthetic methodologies. Key reactions include the hydroboration, widely used for anti-Markovnikov hydrations and reductions of carbon-carbon double or triple bonds (see 1.2.2.1, page 20).<sup>[62]</sup> Perhaps most notably, the Suzuki–Miyaura reaction (**Scheme 17**, a) has been applied extensively because of operational simplicity, the convenient *in situ* activation of the borylated partner, and the range of arylboronic esters and acids that are commercially available.<sup>[63]</sup> The Matteson homologation (**Scheme 17**, b) allows the chain extension of organoboranes,<sup>[64]</sup> and the multi-component Petasis reaction (**Scheme 17**, c) uses boronic acids to form amines.<sup>[65]</sup> The Chan-Lam coupling (**Scheme 17**, d) is another important transformation, facilitating C-N, C-O, and C-S bond formation.<sup>[66]</sup> These reactions, among others, showcase boron's central role in building complex organic molecules efficiently and selectively.



**Scheme 17:** Selected examples of boron-based reactions.

Beyond their synthetic prowesses, boron-containing compounds have also been studied for their biological applications. Boron is considered beneficial in human and animal nutrition, but it has not been classified as an essential micronutrient because its biological role has not been clearly defined yet. Interplays between boron properties and medicinal chemistry include the neutron capture therapy for the destruction of cancerous cells,<sup>[67]</sup> and the probing of sugar for enabling the development of glucose responsive insulin release technologies.<sup>[68]</sup> These last decades also witnessed the emergence of boron containing drugs (**Figure 6**).<sup>[69]</sup> The approval of bortezomib **55** by the FDA (The United States Food and Drug Administration) was a significant achievement made by Millennium Pharmaceuticals.<sup>[70]</sup> Distributed under the name of Velcade, this boronic acid-containing peptide is an injectable treatment for multiple myeloma. In 2015, Takeda Pharmaceuticals received FDA-approval to market the prodrug ixazomib citrate **56** (marketed Sarclisa), targeting the same disease.<sup>[71]</sup> A boronic ester is present on the molecule, and has the benefit of being orally taken instead of injectable. The cyclic borole group also has garnered the efforts of pharmaceutical companies. In 2017, the FDA approved vaborbactam **57** (commercialized as Vabomere), in combination with Meropenem, as a novel non- $\beta$ -lactam antibiotic that inhibits  $\beta$ -lactamase.<sup>[72]</sup>

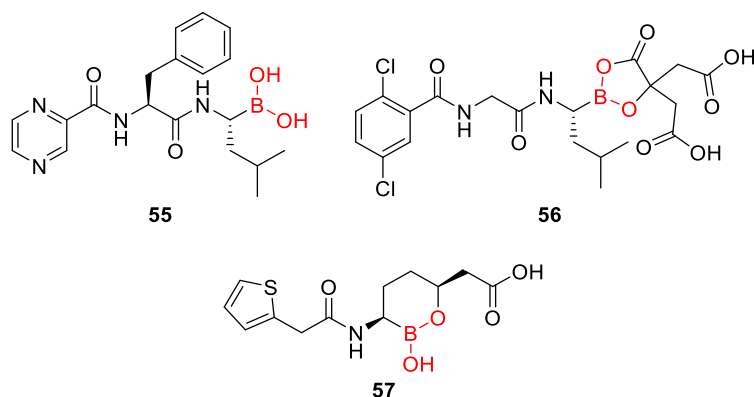


**Figure 6:** Selection of boron containing drugs.

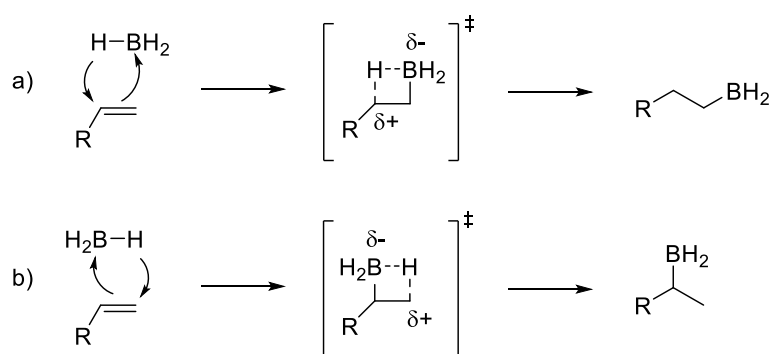
### 1.2.2. Vinylboronates and their existing syntheses

As demonstrated above, boron containing molecules display many properties of interest, and have been proven to be compatible with human biology. Therefore, boron chemistry appears as a potentially fruitful partner for the field of *exo*-glycals, both for biological applications and as a platform for further functionalization. To lay the foundations of the borylated *exo*-glycals study, one would first need to synthesize such molecule bearing a vinylboronate, also named alkenylboronate. Compounds comprising Csp<sup>2</sup>-B bond, as aromatic or alkenyl derivatives, rapidly became extremely popular for the development of different transformations, in terms of both creating complex molecules that include the boron group in the final structure and as a synthetic intermediate for subsequent derivatization,<sup>[73]</sup> such as the Suzuki-Miyaura cross-coupling.<sup>[74]</sup> In consequence, a plethora of new methodologies for the formation of vinylboronates have been developed.

#### 1.2.2.1. Borylation of alkyne

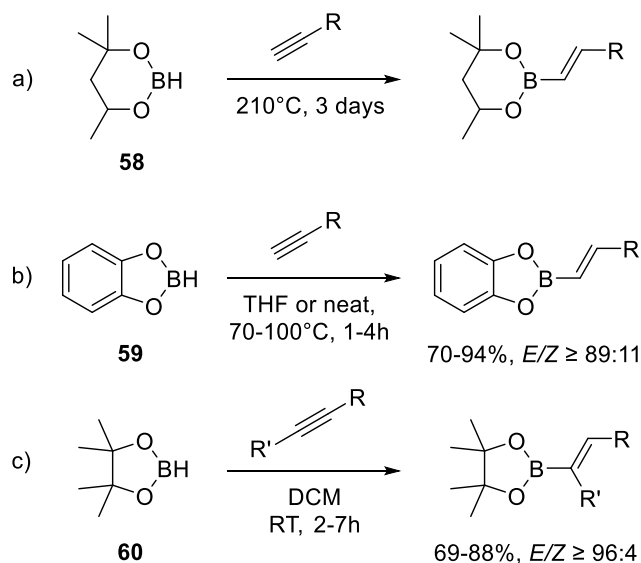
During their work on borohydride reductions, Brown and Rao observed an unexpected borylation side-reaction. This discovery led to the development of the hydroboration of alkene.<sup>[75]</sup> While originally diborane B<sub>2</sub>H<sub>6</sub> was used, the observed catalytic effect of ether motivated the use of complexed borane such as BH<sub>3</sub>.THF. The charge developed in the transition states explain the regioselectivity of the hydroboration. Being electrophilic, the borane is attacked by the  $\pi$ -electrons of the alkene thus leaving either

the substituted or terminal carbon of the alkene electroneficient. Due to the stabilizing effect of the alkyl substituents the first transition state (**Scheme 18**, a) has a lower energy than the second (**Scheme 18**, b) thus the addition of B–H over an unsaturated bond occurred with syn-selectivity and proceeded in an anti-Markovnikov manner.<sup>[76]</sup> The regioselectivity can also be affected by the nature of the solvent and the substituents on the carbon-carbon double bond. Steric consideration also arises with more hindered boron reagents.



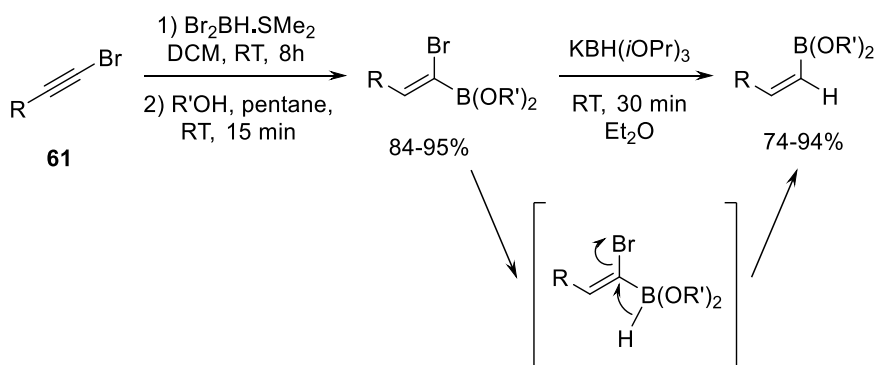
**Scheme 18:** Regioselectivity of the hydroboration.

The first hydroboration of alkyne was the result of Wood's work in 1966.<sup>[77]</sup> Using 4,4,6-trimethyl-1,3,2-dioxaborinane **58**, this protocol required three days of heating at 210°C (**Scheme 19**, a). Milder conditions were developed owing to the introduction of catecholborane **59** by Brown and Gupta (**Scheme 19**, b).<sup>[78]</sup> Despite being the dominant reagent for hydroboration during twenty years, the instability of the catechol boronate group led Knochel and its group to report the use of pinacolborane **60**.<sup>[79]</sup> The reaction runs at room temperature to affords *E*-boronates in good yields with both terminal and internal alkynes (**Scheme 19**, c).



**Scheme 19:** Hydroboration using alkoxyboranes.

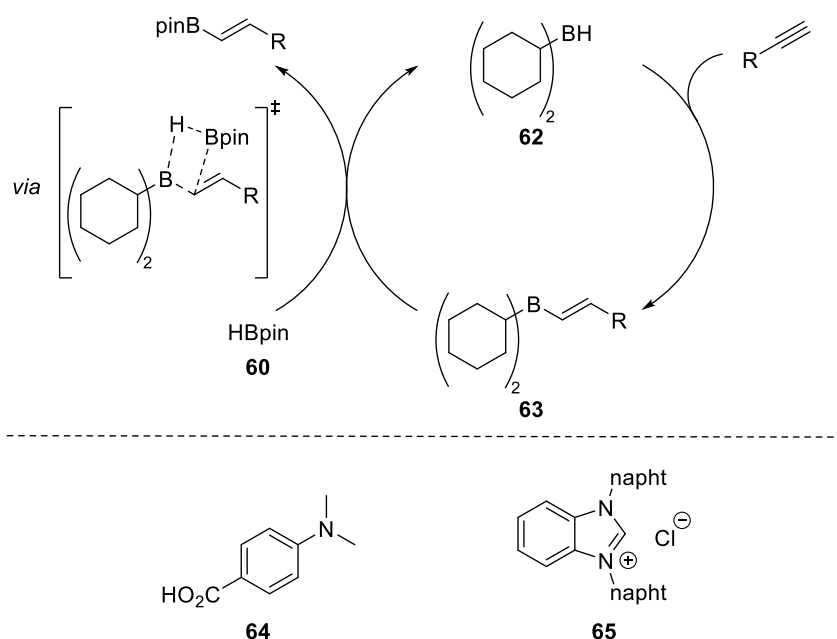
Due to the *syn*-addition of the borane, the hydroboration of alkyne yields the *E*-alkene. Brown reported a two-step procedure to form the more elusive *Z* counterpart.<sup>[80]</sup> Using a pre-functionalized bromoalkyne **61** and a dibromoborane, the *E*-vinylboronate is obtained (**Scheme 20**). The hindered potassium triisopropoxyborohydride triggers a hydride transfer driven by the precipitation of KBr. The *Z*-vinylboronate is obtained as the only isomer.



**Scheme 20:** Synthesis of *Z*-vinylboronate by hydride transfer.



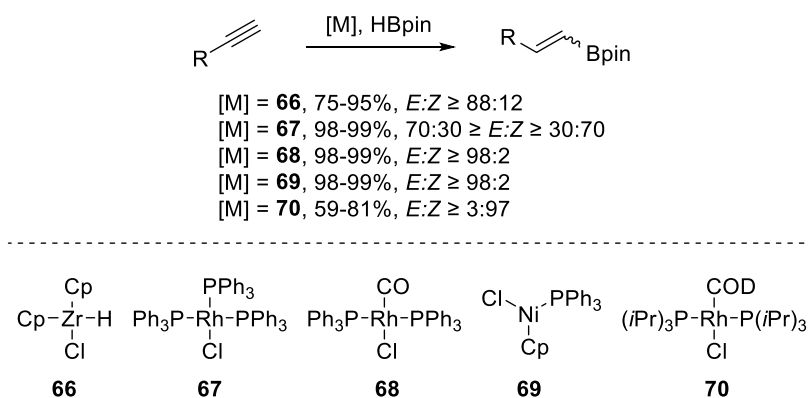
The first catalyzed hydroboration of an alkyne demonstrates a boron to boron alkenyl group transfer. Stoichiometric quantities of either catecholborane **59** or pinacolborane **60** react rapidly with terminal alkynes at room temperature in the presence of a catalytic quantity of the dicyclohexylborane **62** (**Scheme 21**). Mechanistic proposals involve initial hydroboration of the alkyne with dicyclohexylborane to give an alkenyl dicyclohexylborane **63**. The boronic ester is generated after alkenyl transfer from boron to boron in a four membered transition state, which concomitantly restores the dialkylborane catalyst **62** *via* hydride transfer. The higher reactivity of dialkylboranes over dialkoxyboranes was suggested to explain the catalytic process.<sup>[81]</sup> Other metal-free catalyses options include Jin's work with carboxylic acid **64**,<sup>[82]</sup> and Sun's use of NHC generated *in situ* from **65** and DBU.<sup>[83]</sup>



**Scheme 21:** Organocatalysis of the hydroboration of alkynes.

Along with the metal-free protocols, an array of various transition metals has been exploited successfully in the metal-catalyzed hydroboration of alkynes. Earlier work was developed by Srebnik in 1995 with the Schwartz reagent **66**, a zirconium complex, leading to good yield and satisfying selectivity (**Scheme 22**).<sup>[84]</sup> They later reported the first

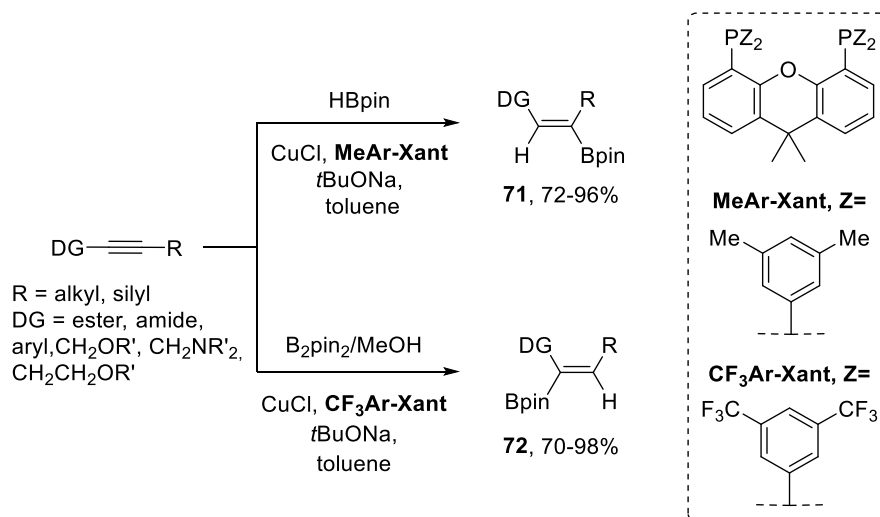
examples using rhodium or nickel complexes. While the use of Wilkinson's catalyst  $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$  **67** evidently improved the yield, the selectivity observed was mediocre. The influence of the ligand was clearly put to light when using  $[\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}]$  **68**. While the yield remained near quantitative, the selectivity was observed to be almost total for the *E* isomer. Nickel catalyst  $[\text{NiCp}(\text{PPh}_3)\text{Cl}]$  **69** was used with similar outcome.<sup>[85]</sup> Remarkably, a complete reversal of selectivity could be achieved in the presence of a  $\text{Rh}(\text{I})\text{-P}(\text{iPr})_3$  complex **70** and  $\text{Et}_3\text{N}$ . Miyaura *et al.* showed that dominant factors to obtain highly pure *Z*-vinylboronate with good yields were an excess of both the alkyne and  $\text{Et}_3\text{N}$  over the borane reagent, as well as the steric and electronic effects of  $\text{P}(\text{iPr})_3$ . Deuterium labeling experiments indicated that the hydrogen atom from the borane ends up in geminal position to boron, which implies a hydride shift from the terminal alkyne.<sup>[86]</sup>



**Scheme 22:** Early examples of metal catalysis of the hydroboration of alkynes.

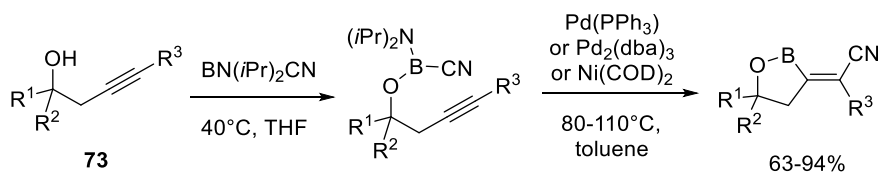
Copper-based catalysts of different natures have also been extensively used in this transformation over the last decade. This approach was first introduced by Miyaura *et al.* who used  $\text{CuCl}$ ,  $\text{AcOK}$  and bis(pinacolato)diboron ( $\text{B}_2\text{pin}_2$ ) and provided a mixture of *E*-vinylboronate **71** and  $\alpha$ -vinylboronate **72** species (**Scheme 23**).<sup>[87]</sup> Higher level of substitution can be achieved by exploiting internal alkynes as substrates. The work of Yun *et al.* resulted in the hydroboration of alkynes bearing various alkyl, aryl and ester groups using  $\text{CuCl}$  and  $\text{P}(\text{otolyl})_3$  with a total selectivity toward the *E* product.<sup>[88]</sup> A striking demonstration of this

chemistry was reported by the group of Tsuji.<sup>[89]</sup> The regioselectivity was successfully controlled by the choice of catalytic species, copper hydride or boryl copper, respectively obtained from HBpin and B<sub>2</sub>pin<sub>2</sub>. This method however requires xantphos derivative ligands, and the presence of a directing group (aryl, ester, amide, etc.) on the alkyne.



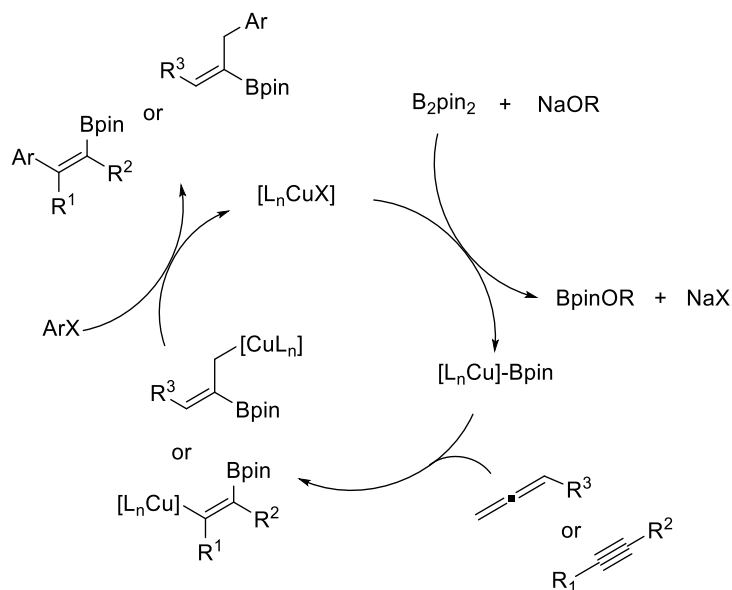
**Scheme 23:** Divergent copper-catalyzed hydroboration of alkynes.

In order to reach a high degree of substitution during the synthesis of alkenylboronate, carboboration was developed, with the concomitant addition of a boron group and a carbon group (instead of the hydride of the hydroboration). The olefins thus obtained were trisubstituted when the reaction is applied to terminal alkynes, and tetrasubstituted when it proceeded using internal alkynes or allenes. The group of Suginome pioneered this work with their pallado-catalyzed intramolecular cyanoboration of homopropargylic alcohols **73** (**Scheme 24**).<sup>[90]</sup> Successful catalysis by Ni(COD)<sub>2</sub> was also reported in the same paper. Later work focused on broadening the scope of alkynes and liberation from the necessary alcohol group on the substrate.<sup>[91]</sup>



**Scheme 24:** Original work on carboboration by Suginome.

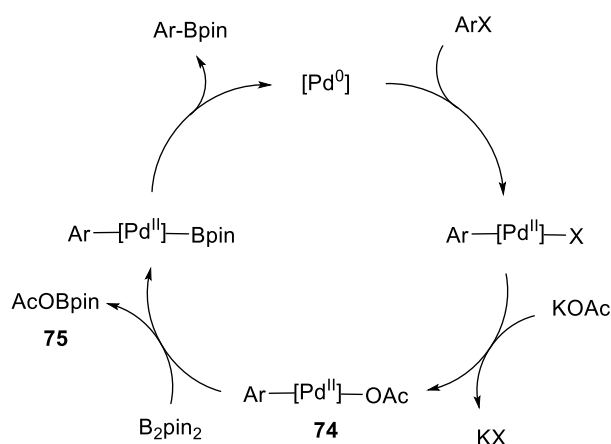
While several other palladium or nickel catalyzed carboborations were reported, copper complexes are still the most successful catalysts for this transformation. These three-components reactions typically involve an alkyne, a borylating agent, and an electrophilic carbon. The versatility of the copper catalyzed carboboration relies on the variety of easily accessible electrophilic carbon compounds, such as halogenoalkane and halogenoarene. An elegant example of such a reaction was disclosed by Brown *et al.*<sup>[92]</sup> In this case, CuCl in combination with tricyclohexylphosphine was found to be the optimal catalytic system (**Scheme 25**). The proposed mechanism involves the initial borylation of the copper center. A vinyl-copper bond is then generated by a migratory insertion of a Cu/Bpin complex across an alkyne or an allene. A cross-coupling reaction with an aryl iodide released the tri- or tetrasubstituted alkenylboronate.



**Scheme 25:** Catalytic cycle of the three-component copper catalyzed carboboration.

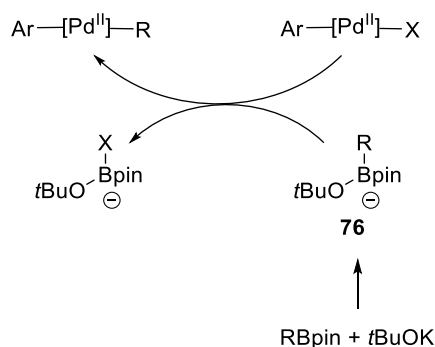
#### 1.2.2.2. Miyaura borylation

Boronic esters can be handily prepared *via* the palladium catalyzed Miyaura borylation. The reaction is highly functional group tolerant and uses commercially available starting materials, allowing access to a wide variety of substrates. The transformation is mechanistically related to the Suzuki–Miyaura coupling in that it proceeds through the  $Pd(0)/Pd(II)$  manifold: oxidative addition of the organohalide, followed by reaction with a base and transmetalation with the diboron reagent, and finally reductive elimination (**Scheme 26**).<sup>[93]</sup> The reaction proceeds at 80°C, and the rate is improved in polar solvents, and with iodide compounds instead of brominated ones.



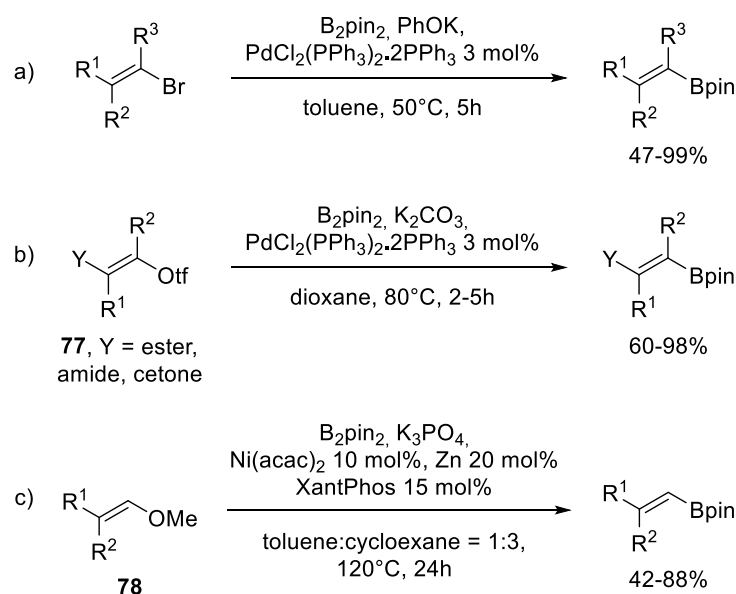
**Scheme 26:** Catalytic cycle of the Miyaura borylation.

With the advancement of the reaction, borylated arene builds up in a media containing aryl halide and palladium. Bisaryl compounds were observed in up to 60% yield as a result of the competitive Suzuki-Miyaura coupling. The key factor to suppress this side reactivity is the choice of the base, suggesting that the transmetalation step is the one controlling the selectivity.<sup>[94]</sup> Indeed, while the well-studied oxidative addition and reductive elimination are identical in both processes, the transmetalation is where they differ. In Suzuki-Miyaura coupling, the base adds to the boron reagent to form a quaternary boronate **76** to encourage the transfer of the R group to the palladium (**Scheme 27**). Strong coordinating bases are generally selected to obtain **76**. Instead, weak nucleophilic bases such as  $KOAc$  are chosen to promote the Miyaura borylation.  $^{11}B$  NMR established that coordination of the acetate onto the boron to form a boronate species did not occur before transmetalation. Therefore, the only accepted activity of the base in the catalytic path is the displacement of the halide. The palladium-halide bond (hard Lewis acid/soft Lewis base) is replaced by a more reactive oxopalladium complex **74** (hard Lewis acid/hard Lewis base). This disfavored transformation is driven by the subsequent generation of acetoxyboronate **75** (**Scheme 26**). This species is not reactive, meaning that only half of the diboron reagent is converted to the boronic ester. However, the pinacolborane ( $HBpin_2$ ) can be directly employed, thus rendering it a more atom-economical procedure.<sup>[94]</sup>



**Scheme 27:** Transmetalation step of the Suzuki-Miyaura cross-coupling.

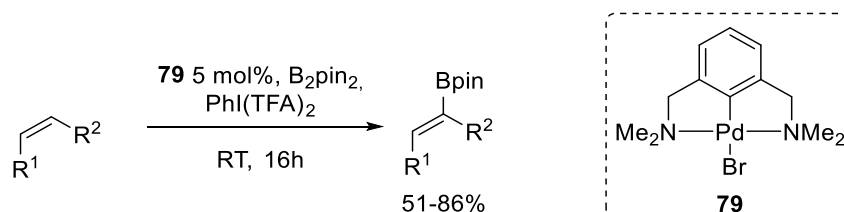
While the initial focus was on the conversion of aryl halides, this transformation was later extended to vinyl halides. Miyaura *et al.* had to tweak their reaction conditions to avoid multiple side products. Similar to the case of aryl halides, a competitive Suzuki-Miyaura can arise between the product and the reagent, but the same partners can also undergo a Heck coupling. A stronger base, KOPh, was necessary to increase the selectivity and obtain satisfying yields (**Scheme 28**, a).<sup>[95]</sup> In a further evolution of their work, the same group reported the use of a triflate group instead of the typical halides. Additional modifications of the conditions were necessary due to the strong KOPh base performing ester exchange with the triflate, generating phenyl triflate. Miyaura settled for K<sub>2</sub>CO<sub>3</sub>, although this base did not allow for the complete shutdown of the Suzuki-Miyaura side reaction. Despite this drawback, their method was still appealing when applied to the synthesis of  $\beta$ -boryl- $\alpha,\beta$ -unsaturated carbonyl compounds **77** (**Scheme 28**, b).<sup>[96]</sup> A related method was reported recently by Lin *et al.* regarding the borylation of enol ether. Methyl ether **78** were converted into vinylboronates with a total *E*-selectivity and average to excellent yields (**Scheme 28**, c).<sup>[97]</sup> A nickel catalyst proved efficient to break the initial C-O bond.



**Scheme 28:** Borylation of functionalized olefins.

#### 1.2.2.3. Borylation via C-H activation of alkenes

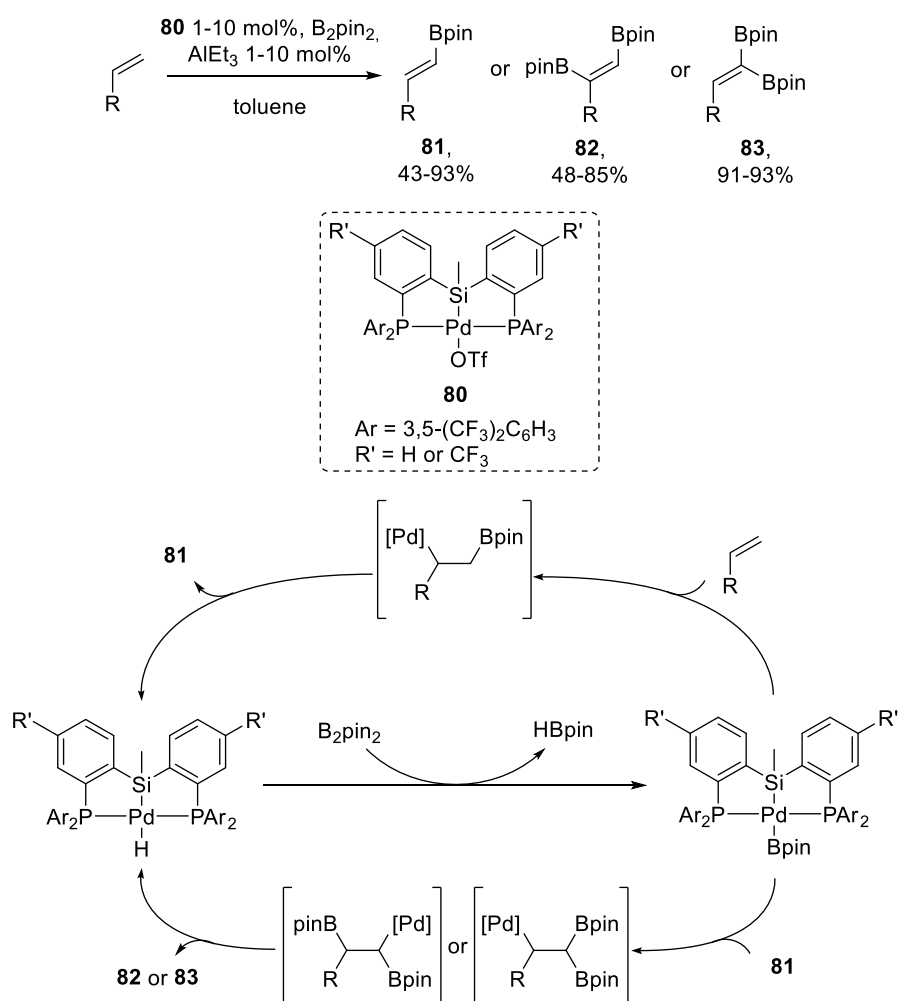
Further atom economies can be achieved through the direct C–H borylation of alkenes. Halide reagents are no longer required since the reaction proceeds from easily accessible unfunctionalized alkenes. In 2010, Szabó *et al.* reported a Pd-catalyzed C–H borylation of alkenes under oxidative conditions. They utilized tridentate NCN-type pincer ligand supported palladium(II) species **79** as catalysts (**Scheme 29**). The critical oxidation to Pd(IV) was achieved via the addition of hypervalent iodine species  $\text{PhI}(\text{TFA})_2$ . The catalyzed borylation reactions occurred conveniently in neat or diluted alkenes at ambient temperature.<sup>[98]</sup>



**Scheme 29:** Borylation of unfunctionalized olefins.

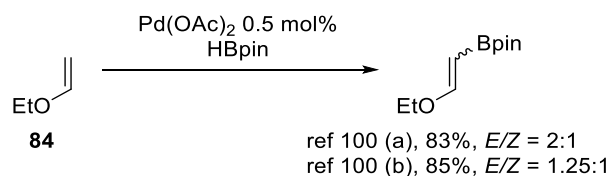


An elegant alternative catalytic system was reported a year later by Iwasawa and his group. Mono or double dehydrogenative borylation of alkenes were achieved in a selective manner using PSiP-pincer ligand supported palladium species **80** (Scheme 30). Although no oxidation of the palladium is necessary, it must undergo transmetalation with  $\text{AlEt}_3$  followed by  $\beta$ -hydride elimination to generate a monohydridopalladium complex. The active palladium catalyst is generated from this hydride species *via* a metathesis process with one equivalent of  $\text{B}_2(\text{pin})_2$ . The insertion of the alkene is followed by a  $\beta$ -hydride elimination process, affording the monoborylation product **81**. When the amount of  $\text{B}_2(\text{pin})_2$  is doubled, the borylated product **81** can enter the catalytic cycle a second time. The insertion step can lead to two regioisomers which release either the  $\alpha,\beta$ -bisboryl alkene **82** or the gem-bisboryl alkene **83**. The chemoselectivity between mono and double borylation is higher than fifty to one. The regioselectivity is controlled by the substituent R on the substrate. The *trans*-bisborylation is favored in most of the reported cases ( $\text{R} = \text{CH}_2\text{R}^1$ ), but the *gem*-bisborylation is observed for  $\text{R} = \text{phenyl}$ , ferrocene, or phthalimide.<sup>[99]</sup>



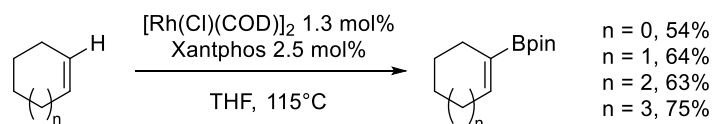
**Scheme 30:** Pallado-catalyzed mono and double borylation of alkenes.

It has to be noted that, on two occasions, the pallado-catalyzed borylation of an enol ether type alkene has been reported in patents.<sup>[100]</sup> Palladium(II) acetate and pinacolborane are mixed with the ethyl vinyl ether **84** in very mild and neat conditions (**Scheme 31**). The corresponding alkenylboronates are obtained in good yield as an *E/Z* mixture. This borylated enol ether has been exploited for the transfert of allylic moieties in metal-catalyzed procedures, including in a Suzuki-Miyaura coupling involved in the total synthesis of alkaloids.<sup>[101]</sup> However, in these reports the alkenylboronate was not synthesized, but simply purchased from commercial sources.



**Scheme 31:** C-H activation and borylation of enol ether.

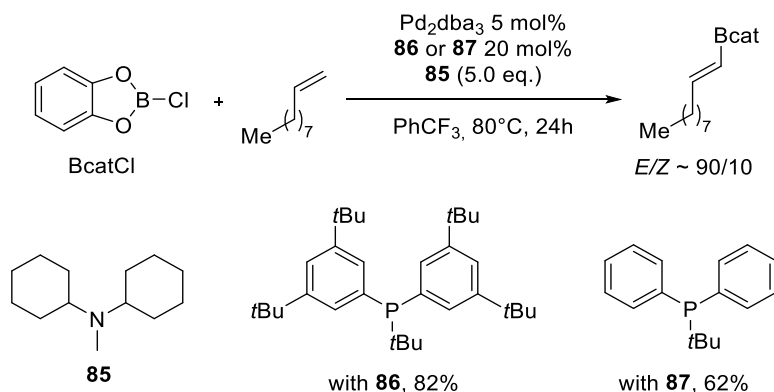
Cyclic alkenes were converted in the rhodium catalyzed dehydrogenative borylation disclosed by Jamison and Kondoh.<sup>[102]</sup> They initially faced issues regarding the undesired hydroboration of alkenes and borylation of allylic C–H bonds. These parasitic side reactions were averted by adjusting the combination of added rhodium precursors and ligands. Cyclic 1-alkenylboronic esters were synthesized directly with high chemoselectivity (**Scheme 32**). The reaction mixture could be involved into a subsequent Suzuki–Miyaura coupling reaction after a simple filtration. Murakami *et al.* applied this rhodium C-H activation strategy to the borylation of linear alkene by replacing the Xantphos ligand with the ferrocene-based Foxap.<sup>[103]</sup> Notably, the catalytic activity of iridium and iron based complexes, as well as cobalt-containing MOF, was demonstrated in dehydrogenative borylation of alkenes.<sup>[104]</sup>



**Scheme 32:** Rhodium-catalyzed dehydrogenative borylation of cyclic alkenes.

The boryl-Heck is another example of borylation via C-H activation of an alkene. Pioneering work by Suginome reported both intra- and intermolecular boryl-Heck reaction.<sup>[105]</sup> Watson *et al.* further extended this strategy. The Watson group has expertise in the silyl-Heck reaction as well as the aza-Heck reaction.<sup>[106]</sup> Notably, the electron-rich phosphine **86** they developed for the silyl-Heck reaction was a key element of their successful catalytic system (**Scheme 33**).<sup>[107]</sup> Both the phosphine ligand and the base **85** must be bulky to disfavor the addition on the electrophilic boron reagent. Although the phosphine **86** gave the best result, it is worth

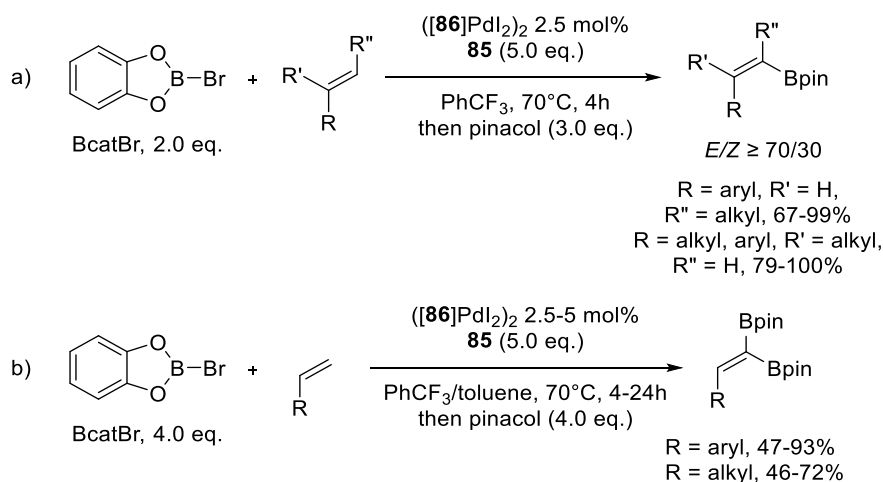
mentioning that the commercially available phosphine **87** yielded a satisfying amount of product.



**Scheme 33:** Watson's optimization work of the boryl-Heck reaction.

The isomerization of the starting terminal olefin accounts for 15-20% of the missing yields. LiOTf was added to suppress this isomerization, making the borylation quantitative when this additive was used in combination with phosphine **86**. When styrene derivatives are used as the terminal olefin, Lil is added instead, to quench the potential polymerization. High yields and good functional group tolerance were both achieved, and substrates were transformed to their corresponding alkenyl boronic esters with excellent *E/Z* ratios. The vinylcatecholboronate products were readily converted to a variety of boronic esters, amides, and borate salts via *in situ* transesterification treatment.<sup>[107]</sup>

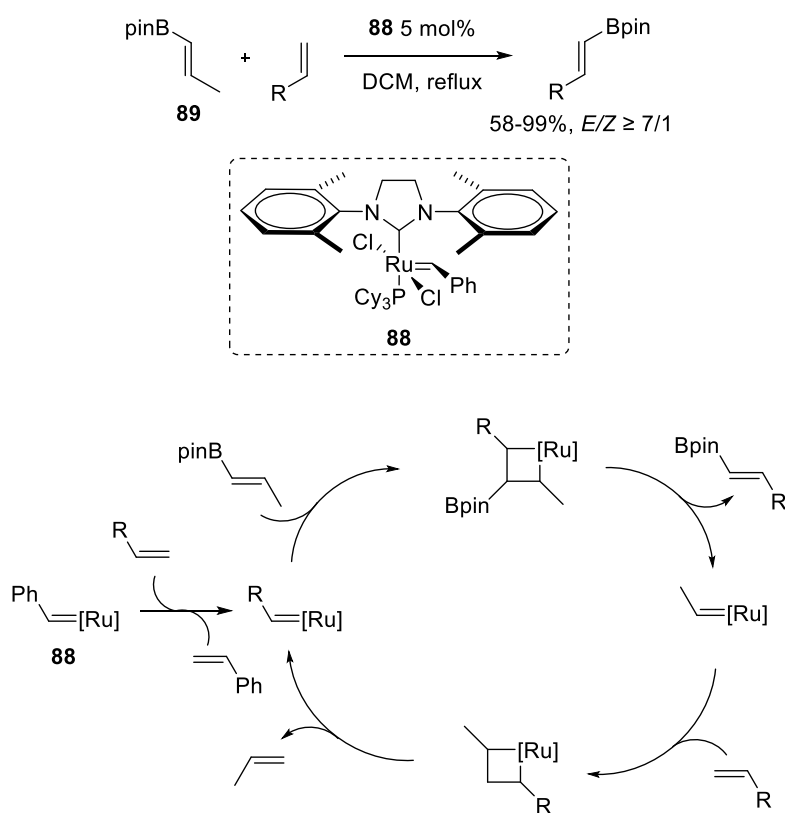
This method was initially limited to monosubstituted terminal alkenes due to the steric hindrance that arises when more substituted olefins are used. However, latter improvements solved this issue. The use of BrBcat, instead of ClBcat, along with the precatalyst (**[86]PdI<sub>2</sub>**)<sub>2</sub> allowed for the borylation of 1,1- and 1,2-disubstituted alkenes (**Scheme 34, a**).<sup>[108]</sup> Similar conditions were subsequently applied to the diborylation of terminal olefins (**Scheme 34, b**).<sup>[109]</sup> For further discussion on the boryl-Heck, see chapter 3.2., page 53.



**Scheme 34:** Further improvement of Watson's boryl-Heck.

#### 1.2.2.4. Olefin metathesis

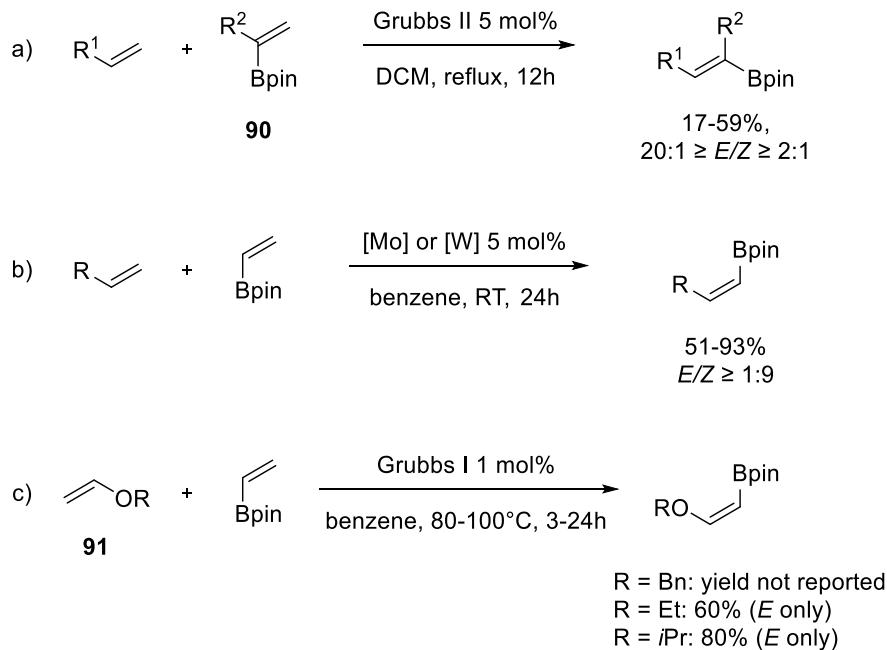
Olefin cross-metathesis, one of the main tools to generate functionalized alkenes,<sup>[110]</sup> has been applied in the preparation of alkenyl boronates. Based on the second-generation ruthenium catalyst **88**, Grubbs and Morrill reported the reactions of 1-propenyl pinacol boronate **89** with a variety of monosubstituted olefins (**Scheme 35**). Satisfactory results were obtained in terms of yields, selectivity, and functional group compatibility.<sup>[111]</sup> Under similar conditions, Burke *et al.* presented the reaction using vinyl MIDA boronate, thereby improving the stereoselectivity of the reaction ( $E/Z > 20:1$ ).<sup>[112]</sup>



**Scheme 35:** Olefin cross-metathesis applied to vinylboronate chemistry.

The same group extended their work to the synthesis of vinylboronates presenting a higher degree of substitution with moderate success. Trisubstituted olefins were obtained via metathesis with  $\alpha$ -substituted boronates **90** (Scheme 36, a). Using 2- isopropenyl pinacol boronate (**90**, R = Me), various alkenes were converted into trisubstituted alkenylboronates in modest yields but with a good selectivity (*E/Z* = 20:1). The reaction proved more challenging with larger substrate (R = alkyl, phenyl).<sup>[113]</sup> A *Z*-selective transformation was reported by Hoveyda *et al* (Scheme 36, b). Products are generated by the use of a tungsten-based complex in up to 91% yield and an excellent selectivity towards the *Z* isomer. The more sterically demanding *Z*-alkenylboron species are obtained in the presence of molybdenum-based catalyst.<sup>[114]</sup> It has to be noted that a few enol ether were reported as substrates of the olefin cross-metathesis (Scheme 36, c). A first-generation Grubbs catalyst was utilized in a patent

authored by Cossy *et al.* to transform a benzyl derivative (**91**, R = Bn) while Marciniec *et al.* exploited the same ruthenium complex for the transformation of alkyl derivatives (**91**, R = Et, *i*Pr).<sup>[115]</sup>



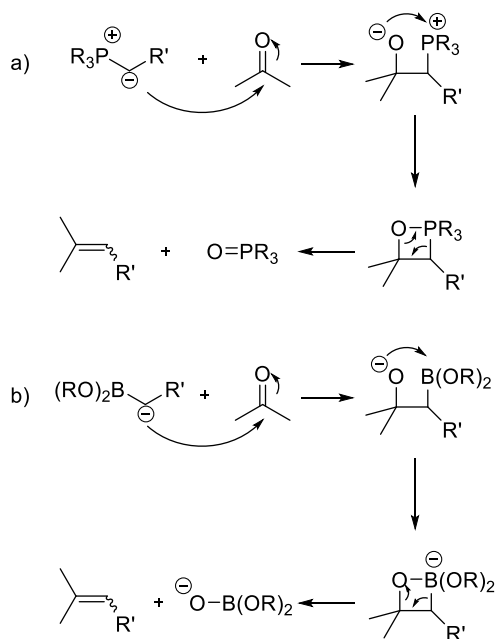
**Scheme 36:** Selected examples of olefin metathesis.

#### 1.2.2.5. Boron-Wittig reaction

The boron-Wittig reaction, as the name suggests, is related to the phosphorus-based Wittig reaction. This connection appears clearly when comparing the mechanisms of both reactions (**Scheme 37**). In each case, the first step is the addition of a reactant, previously deprotonated, to a carbonyl function. The reagent must bear a heteroatom in the alpha position to the carbanion. This role is filled by a phosphonium group in the Wittig reaction, while the use of a boryl group gave its name to the boron-Wittig reaction. The alkoxide<sup>i</sup>, resulting from the addition step, attacks the heteroatom to form a four-membered ring. From this tense cycle, a heteroatom oxide is released, and the desired carbon-carbon double bond

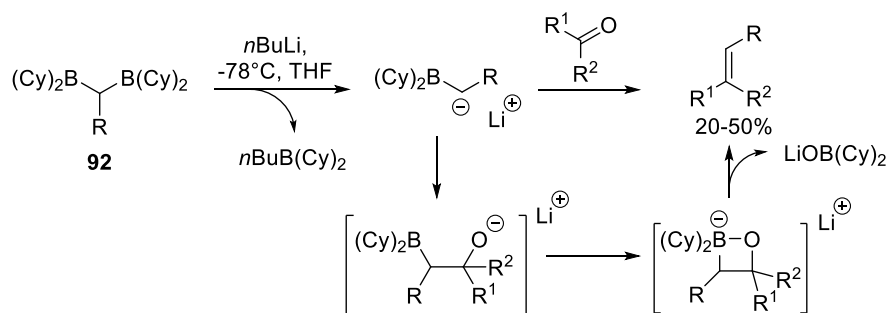
<sup>i</sup> The betaine intermediates are observed when the reaction is carried out in presence of coordinating ion such as lithium.

is created. The formation of these heteroatom oxides is considered to be the driving force of the reaction. If the desired product is an alkene boronate, the R' group should be a borylated one.



**Scheme 37:** Mechanism of the Wittig (a) and boron-Wittig (b) reactions.

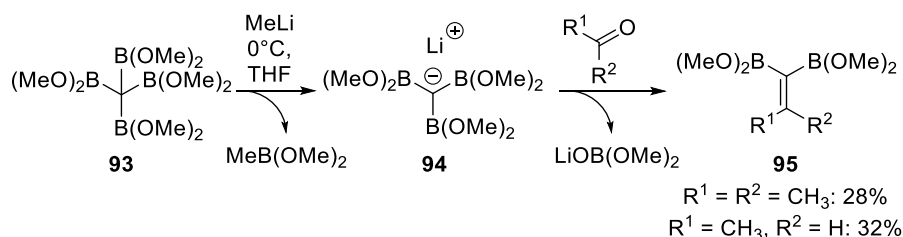
The boron-Wittig reaction was first reported by Zubiani and co-workers, in 1966, using a bisborylalkane **92**, although both of the boryl groups were lost in the process (**Scheme 38**).<sup>[116]</sup> The *n*BuLi-mediated deborylation of 1,1-bis(dicyclohexylboryl)alkanes **92** were followed by a condensation with carbonyl compounds to yield the corresponding olefins.



**Scheme 38:** First boron-Wittig work by Zubiani *et al.*



Matteson and his group extended the boron-Wittig reaction to the synthesis of borylated olefins. They conducted the olefination starting from tetra(dimethoxyboryl)methane **93** in the presence of MeLi (**Scheme 39**).<sup>[117]</sup> The *in situ* generated tris(dimethoxyboryl)methide ion **94** is able to condense with aldehydes and ketones to produce 1,1-bis(boryl)alkenes **95**. They later made use of the more stable pinacol-based boronic esters Bpin for these transformations.<sup>[118]</sup>



**Scheme 39:** Vinylboronate synthesized *via* deborylation.

Rathke and Kow showed that it was possible to generate the anion of B-methyl-9-borabicyclo[3.3.1]nonane by deprotonation using lithium 2,2,6,6-tetramethylpiperide **96** (LiTMP), the steric hindrance of the base preventing its addition onto the boron and hence the deborylation (**Figure 7**).<sup>[119]</sup>

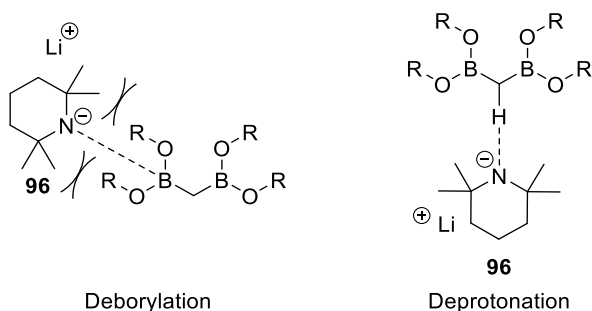
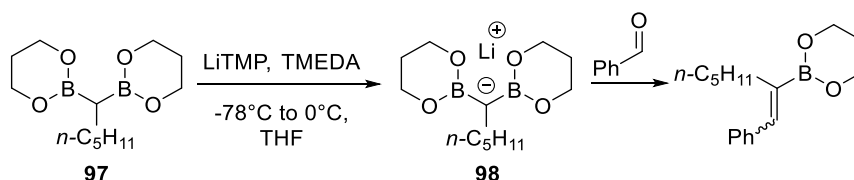


**Figure 7:** Interactions between LiTMP and a bisborylalkane.

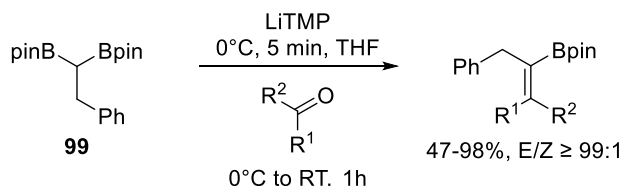
Inspired by this precedent, Matteson and co-workers extended the application of LiTMP to deprotonate methanediboronate reagents **97** to form the corresponding lithium diborylmethide salts **98** in the presence of tetramethylethylenediamine (TMEDA) (**Scheme 40**).<sup>[120]</sup> The subsequent

condensation with aldehydes proved efficient, with the loss of a single boron group.



**Scheme 40:** Vinylboronate synthesized *via* LiTMP deprotonation.

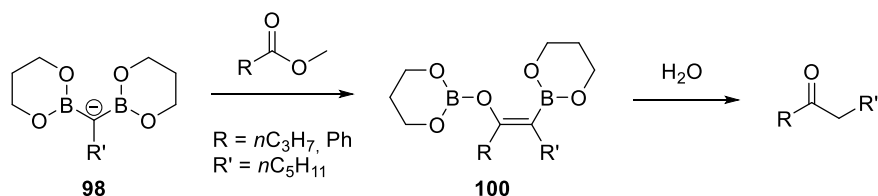
The synthesis of vinylboranes through the boron-Wittig reaction has gained great interest within the last decade, as a synthetic tool, with a significant level of stereochemical control and applications in target compounds.<sup>[121]</sup> Endo and Shibata paved the way for this recent regain of interest with their work on tetra-substituted alkenyl boronates. The convenient LiTMP-triggered deprotonation of a benzylated *gem*-diboryl alkane **99**, bearing pinacolboronic esters, is followed by its addition on ketones (**Scheme 41**).<sup>[122]</sup> The corresponding vinylboronates are obtained in average to excellent yield, with a nearly total selectivity for the *E* alkenes, when the ketone is asymmetrically functionalized. Further discussion on the boron-Wittig reaction can be found in chapter 4., page 63.



**Scheme 41:** Synthesis of tetrasubstituted alkenyl boronates *via* a boron-Wittig reaction.

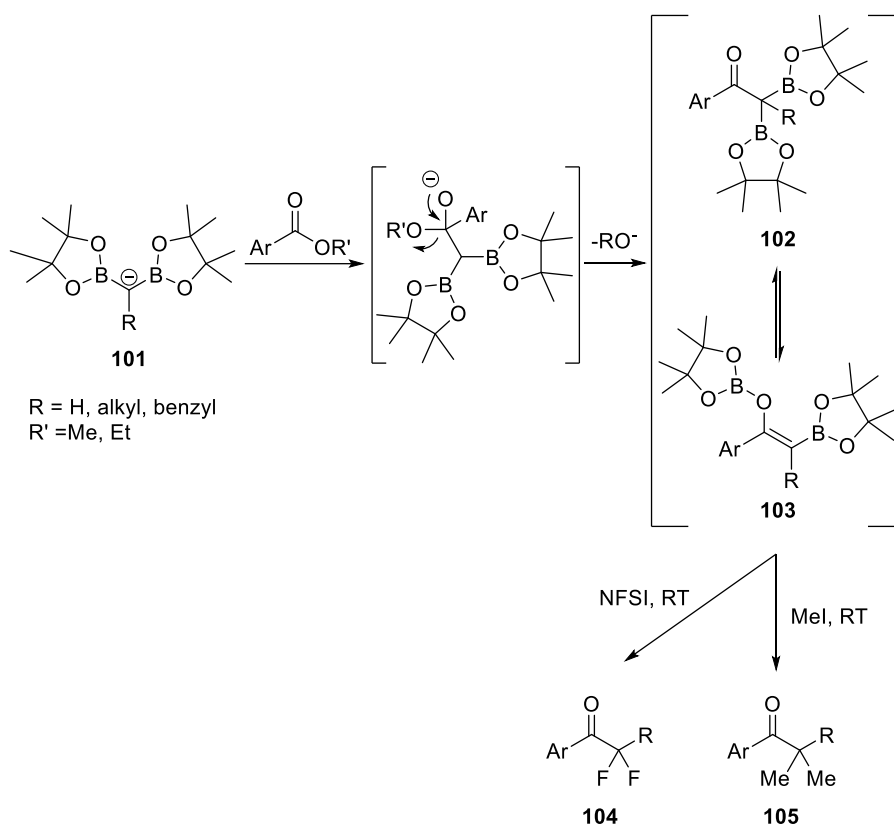
However, when applied to esters and amides, this reaction diverges mechanistically, producing ketones rather than vinylboronates. Matteson was the first to observe this unexpected reactivity.<sup>[120]</sup> While the reaction between the bisboryl carbanion **98** and aldehydes produced the anticipated olefins (**Scheme 40**), applying similar conditions to ester substrates led to the formation of ketones (**Scheme 42**). Matteson postulated the existence of the enol borate intermediate **100** which would be immune to further

attack by the carbanion and would hydrolyze rapidly. Similar findings were reported by Yamaguchi *et al.* using the borane group 9-borabicyclo(3.3.1)nonane (9-BBN).<sup>[123]</sup>



**Scheme 42:** Boron-Wittig reactions on ester by Matteson.

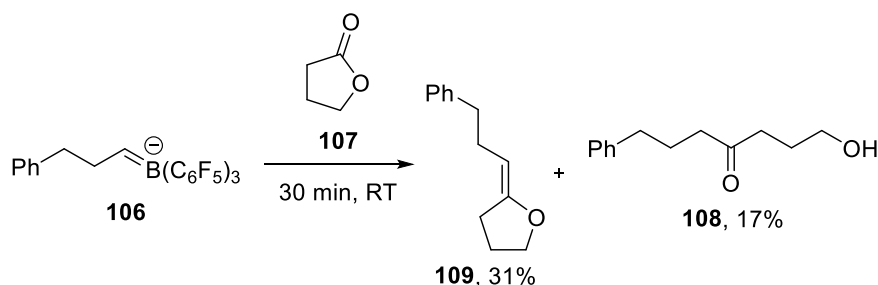
The existence of this enol borate intermediate was later confirmed and exploited by Pattison *et al.*<sup>[124]</sup> In an addition/elimination sequence, the addition of deprotonated bisborylalkane **101** on an ester generates the  $\alpha,\alpha$ -bisboryl ketone **102** *in situ* (**Scheme 43**). This compound is in equilibrium with its enol borate form **103** that can be further doubly trapped by addition of an electrophilic fluorinating reagent such as N-fluorobenzenesulfonimide (NFSI) or MeI.



**Scheme 43:** Trapping of the enol borate intermediate with electrophiles.

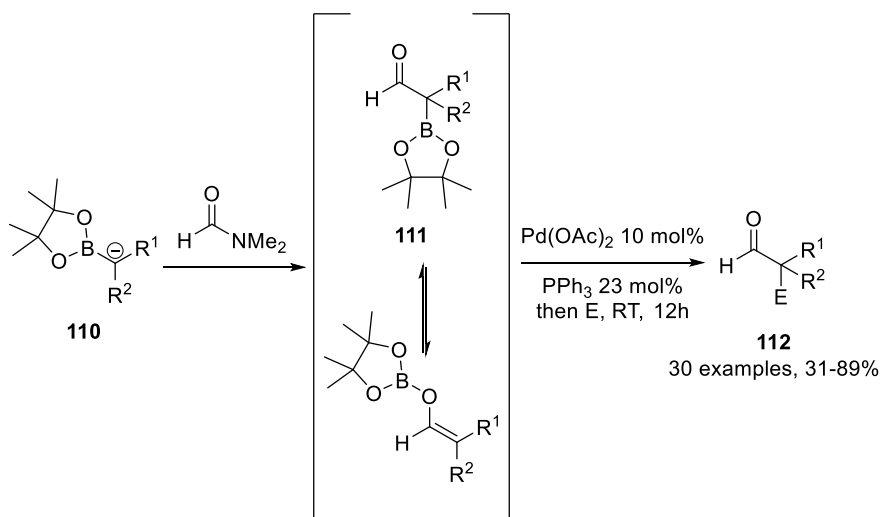
Although the boron-Wittig reaction applied to esters resulted, in most cases, in the formation of a ketone, Erker reported a successful olefination protocol of these substrates.<sup>[125]</sup> The  $\alpha$ -borylcarbanion **106**, generated *in situ* upon deprotonation with LiTMP, reacted with several ketones and, more interestingly, with esters. This procedure was even exemplified on  $\gamma$ -butyrolactone **107**, although a side-product **108** was observed, ensuing from the hydrolysis of the desired product **109** during the work-up (**Scheme 44**). The electron-deficiency of the  $\text{B}(\text{C}_6\text{F}_5)_3$  group is the key factor to explain this reactivity with esters. It increases the acidity of the geminal proton, whereas more common boronic esters (like Bpin) do not allow for the deprotonation of monoborylated alkanes due to their higher pKa. More importantly, the amplified electrophilicity of the boron atom favors the formation of the four-membered ring intermediate (see

**Scheme 37)** and the subsequent elimination over the ring-opening of the lactone leading to the enol borate.



**Scheme 44:** Erker's boron-Wittig on  $\gamma$ -butyrolactone.

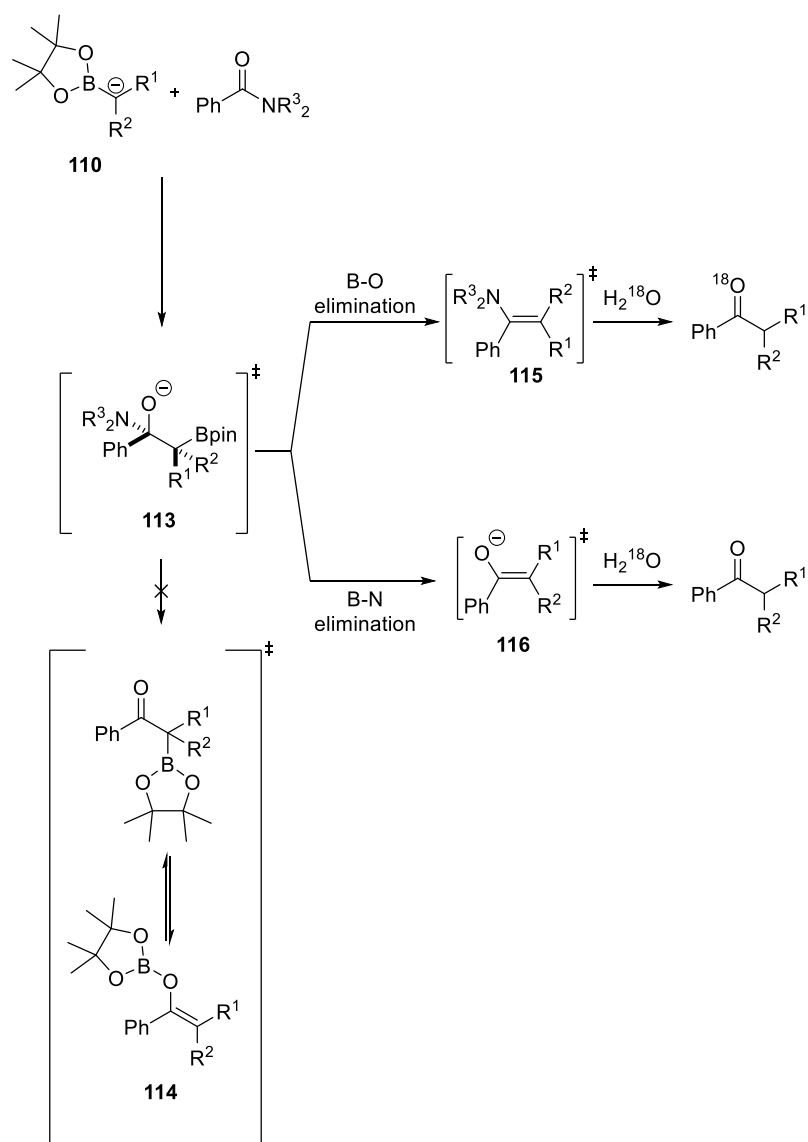
The reactivity of amides under boron-Wittig conditions has been shown to be ambiguous. Xu *et al.* demonstrated that DMF can react with a deborylated bisborylalkane **110** to form an  $\alpha$ -boron aldehyde **111** (**Scheme 45**).<sup>[126]</sup> This stable intermediate, resulting from an addition/elimination sequence, efficiently reacted with electrophilic allylic reagents *via* Pd-catalyzed cross-coupling reaction. This procedure led to products **112** featuring new quaternary carbon centers in average to good yields.



**Scheme 45:** Boron-Wittig reaction carried out on DMF.

The work of Liu *et al.* provides interesting nuances concerning the reactivity of amides towards the boron-Wittig reaction.<sup>[127]</sup> The deborylated bisborylalkane **110** ( $R^1 = H$ ,  $R^2 = (CH_2)_2Ph$ ) was added to primary, secondary, and tertiary amides to form the alcoholate **113** (**Scheme 46**). In contrast to the respective works of Matteson, Pattison and Xu, the elimination leading to enol borate **114** is not considered. Instead, the formation of a four-membered ring and the B-O elimination (see **Scheme 37**) leading to enamine **115** is proposed. A rotation around the central carbon-carbon single bond could also position the amine group in front of the boron, thus paving the way for the B-N elimination as an alternative pathway. Upon hydrolysis, both the enolate **116** and the enamine **115** would lead to the same ketone product.

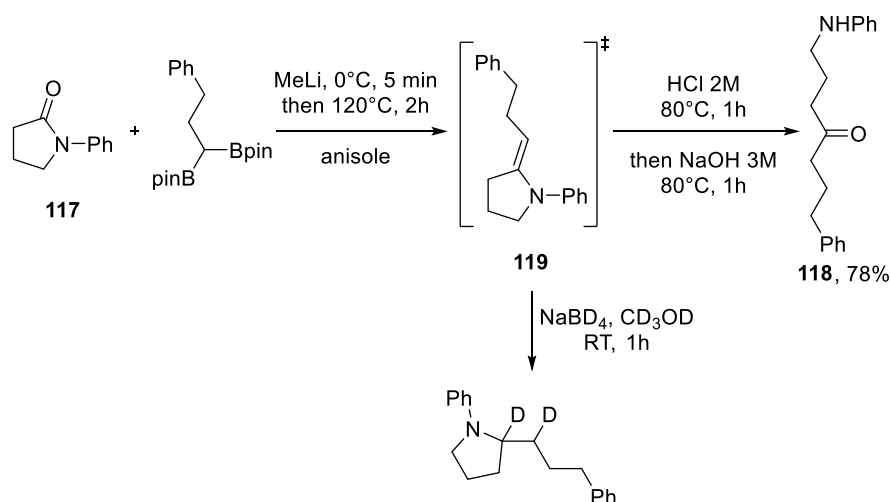
To discriminate between these two routes,  $^{18}O$  isotope-labeled water is used. While the hydrolysis of enamine **115** incorporates the labeled oxygen atom, the product of the hydrolysis of enolate **116** retains the oxygen atom originally borne by the amide. When the reaction was carried out on primary and secondary amides, the ketone product was  $^{18}O$ -labeled, indicating its formation through the standard boron-Wittig mechanism involving the B-O elimination. For tertiary amides however, the unlabeled ketone was obtained as the sole product. Liu *et al.* concluded that the B-N elimination occurred, but one should note that the hydrolysis of **114** with labeled water would also lead to the unmarked ketone.



**Scheme 46:** Boron-Wittig reaction on amide and subsequent isotope labelling experiment.

Liu *et al.* applied their conditions to various primary, secondary and tertiary amides using an electrophile (instead of water) to trap the intermediate enolate/enamine. Among the compounds synthesized this way, our interest was piqued by the use of lactam **117** as a substrate. While the research team was expecting the formation of  $\gamma$ -aminoketone **118**, they

were surprised by the strong hydrolysis conditions required to obtain this product (**Scheme 47**). They postulated that lactam **117**, unlike the open-chained tertiary amides, follows the B-O elimination pathway, typical of the boron-Wittig. The  $\gamma$ -aminoketone **118** would be obtained from the hydrolysis of an enamine intermediate **119**, a claim that was later supported by means of a reduction procedure using deuterated sodium borohydride.



**Scheme 47:** Boron-Wittig reaction of lactam **117** and deuteration experiment.

The boron-Wittig reaction has demonstrated great efficiency in the conversion of ketones and aldehydes into borylated alkenes. However, not unlike other olefination methods, the conversion of esters and amides proved to be significantly more challenging, with only few successes reported, and none leading to a vinyl boronate. Across the varying methodologies reported for the boron-Wittig reaction, a common feature remains: the use of a borylated alkane reagent.



## 2. Objectives and strategies

The family of *exo*-glycals has been the focus of many research groups, among them the Stephane Vincent group (UNamur), our partner on this project. The potential therapeutic applications of those molecules was demonstrated and reviewed recently by Vincent and Frédéric.<sup>[58]</sup> Although the biological activity of the *exo*-glycals appeared to be correlated to the functionalization of the double bond by an electron-withdrawing group, to the best of our knowledge, no example of borylated *exo*-glycal has been reported.

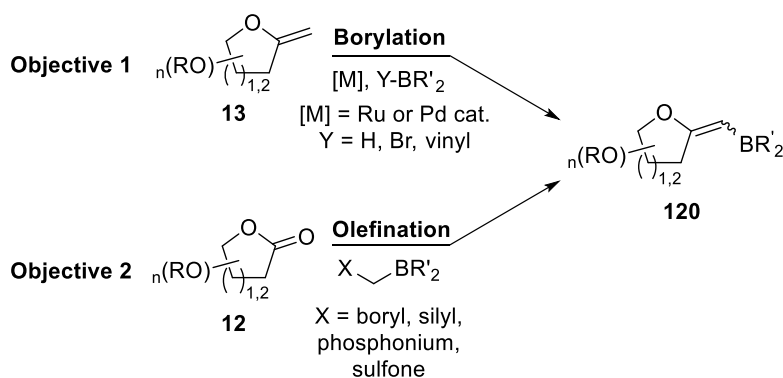
Accordingly, the global objective of this thesis is the synthesis of the first borylated *exo*-glycals **120**. These compounds could later be evaluated for their biological potency or their use as key intermediates, given the broad spectrum of transformations enabled by the boron moiety.

In chapter 1.1, we looked into the existing methods to synthesize *endo*- and *exo*-glycals for inspiration. While some reports treat of double bond functionalization, these protocols are generally specific and difficult to adapt to boron chemistry. Olefination process from sugar lactones, either through a modified Julia olefination or a combined addition-elimination strategy, have been shown to be more versatile. A suitable borylated nucleophilic partner could allow us to exploit these methods for the synthesis of borylated *exo*-glycals.

The most commonly used pathways to vinylboronates were covered in chapter 1.2. Most of the literature focuses on the borylation of alkynes. This strategy however is not adapted to the synthesis of (*exo*-)cyclic double bonds. The Miyaura borylation, the olefin metathesis and the C-H activation strategy all rely on a pre-existing alkene. The boron-Wittig reaction, on the other hand, permits the use of carbonyl substrate. It has to be noted that very few reported syntheses of vinylboronates includes substrates bearing an *exo*-cyclic double bond, an enol ether type of double bond, or protecting groups typical of the sugar chemistry.

According to these observations, we set ourselves the following two objectives (**Scheme 48**):

- 1) The synthesis of borylated *exo*-glycals **120** by the direct borylation from a pre-formed methylene *exo*-glycals **13**.
- 2) The development of an olefination strategy of sugar lactone **12** using a boron containing partner.



**Scheme 48:** General objectives of this work.

**Objective 1.** Borylation strategies necessitate the preliminary formation of a methylene derivative **13**. Although these compounds are unstable and represent a drawback of the borylation pathway, their synthesis are well described, using Petasis' reagent for example.<sup>[27]</sup> Recent publications by both Watson and Bolshan led us to consider the boryl-Heck reaction as a viable route to borylated *exo*-glycals.<sup>[128-129]</sup> It was also reported that olefin metathesis strategies were compatible with vinylboronates, enol ethers and benzyl protecting groups (*vide supra*). These are key features of the borylated *exo*-glycals, demonstrating the potential applicability of the olefin metathesis as a synthetic method. The focus of these studies will be on the catalytic system, the conditions of the reactions, as well as the nature of the sugar substrate.

**Objective 2.** The olefination strategies have the advantage to build on commercially available or readily available, sugar lactone substrates. The boron-Wittig reaction has been exploited with success for the synthesis of vinylboronates, but never applied to *exo*-glycal chemistry. On the other hand, Wittig and Julia olefinations are central in *exo*-glycal chemistry, but absent of the reported borylation options. The silicon-based Peterson olefination was also used once for the synthesis of an *exo*-glycal, and on several occasion to generate alkenyl boronate. In each of those olefination

methods, a borylated partner is needed. It must comprise a central carbon to create the *exo*-cyclic C-C double bond, a boron group which must be conserved in the final molecule, and a sacrificial group which elimination will drive the process (**Figure 8**). The type of reaction depends on the nature of the sacrificial group. For the boron-Wittig, a second borylated group plays that role. The *gem*-diboryl alkane **121** has been reported and used in many cases. *Gem*-silylboryl alkane **122** was reported on a few occasions, and would correspond to a Peterson olefination. Phosphonium salt **123** was reported once, and the following attempt at using it in a Wittig reaction failed. The modified Julia reaction is probably the most convenient olefination method for *exo*-glycal synthesis (*vide supra*). A borylating version of this reaction would require the *gem*-sulfonylboryl alkanes **124**. However, to the best of our knowledge, these compounds have never been reported.

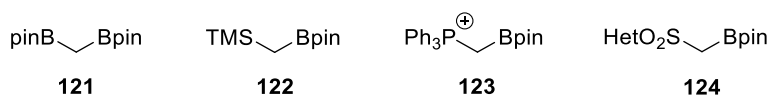
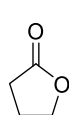


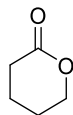
**Figure 8:** Boron reagents for the olefination methods.

The synthesis of these borylated partners is a key step to be able to assess to applicability of the olefination methods to the formation of borylated *exo*-glycals. Accordingly, the first task for achieving Objective 2 will consists in the synthesis of **121-123** and the development of a synthesis for **124**. The reaction of these latter with various carbonyl compounds will then be considered (**Figure 9**). Simple lactones  $\gamma$ -butyrolactone **107** and  $\delta$ -valerolactone **125** will be used as five- and six-membered ring model substrates. More complex sugar lactones like **126-128** are also considered to study the impact of features such as the ring size, the nature of the protecting groups, or the stereochemistry of the substrate. In the case of the reagent **122**, for which a boron-Wittig/Peterson chemoselectivity issue may arise, the experimental work will be supported by means of computational studies.

Model substrates:

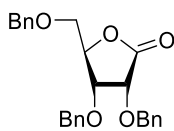


**107**

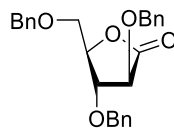


**125**

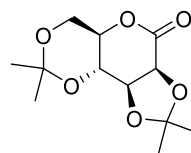
Example of sugar lactones:



**126**



**127**



**128**

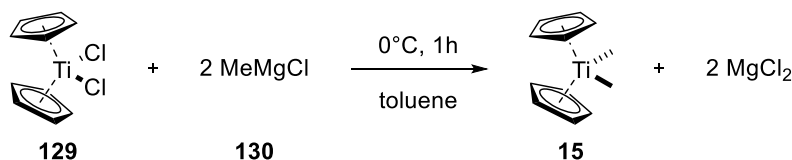
**Figure 9:** Examples of carbonyl substrates envisaged for this work.

### 3. Borylation of methylene *exo*-glycols

#### 3.1. The methylene *exo*-glycols

Our first objective is aimed at the borylation of a preformed *exo*-glycol. The boryl-Heck reaction and the olefin metathesis are considered for this transformation. While the nature of the borylating agent and the catalytic system vary between these two pathways, they are both relying on the same substrates: methylene *exo*-glycols **13**. These unsubstituted *exo*-glycols are well documented and have been discussed previously (see chapter 1.1.2.1, page 6). Several reactions have been used to achieve their synthesis, among which are the Tebbe olefination, the Petasis olefination, the modified Julia olefination and the Ramberg-Bäcklund reaction. The metallocene-based methods were deemed more practical. Among them, we selected the Petasis olefination, for which the reagent **15** is more stable than its pyrophoric Tebbe counterpart **14**.

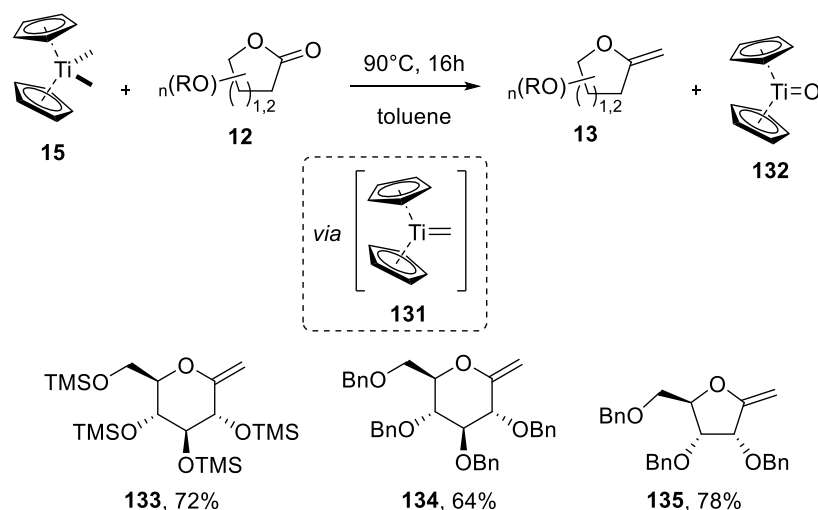
The Petasis reagent can be synthesized in one step from commercially available titanocene dichloride **129**. While Petasis originally performed this transformation using methyllithium,<sup>[28]</sup> a more convenient Grignard-based procedure by Verhoeven *et al.* was subsequently reported.<sup>[130]</sup> In this publication, the titanocene **129** is alkylated via a salt metathesis reaction with methylmagnesium chloride **130** (Scheme 49). The reaction solvent is not completely evaporated after the work-up in order to obtain compound **15** as a solution in toluene, more stable than the pure dried product. We replicated this reported procedure, and the solution's concentrations were assayed by <sup>1</sup>H NMR spectroscopy between 7.5%-15.5% by weight, with an average yield of 86% over five batches.



**Scheme 49:** Synthesis of the Petasis reagent.

Using the Petasis reagent, we converted several sugar lactones into their methylene *exo*-glycol equivalents. Based on a protocol by Vincent *et*

*al.*,<sup>[131]</sup> titanium carbene **131** was generated *in situ* following the thermal activation of **15**. This olefinating agent allowed for the conversion of three sugar lactones into their corresponding methylene *exo*-glycal (**Scheme 50**). The crude mixtures obtained required a purification *via* chromatography to remove the titanocene oxide side-product **132**. However, methylene *exo*-glycals are known for their instability, notably their tendency to isomerize into their *endo* counterpart in an acidic medium. Therefore, neutral alumina was selected as the stationary phase, and the *exo*-glycals **133-135** were obtained in good yields (64-78%). Due to the instability of these compounds, they were stored under argon at 4°C, and used within a week.



**Scheme 50:** Synthesis of methylene *exo*-glycals.

Interestingly, it was observed during the synthesis of **133** that one of the purification fractions was the desilylated side-product **136** (**Figure 10**). The mono-desilylation occurred at the primary alcohol position, which is more sterically accessible. This deprotection might have happened during the synthesis or the purification step. The <sup>1</sup>H NMR spectra of the desired product **133** and the side-product **136** are too similar to be discriminated in the crude. Nevertheless, this observation indicates that the TMS group may prove to be insufficiently robust as a protecting group.

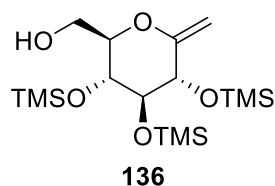


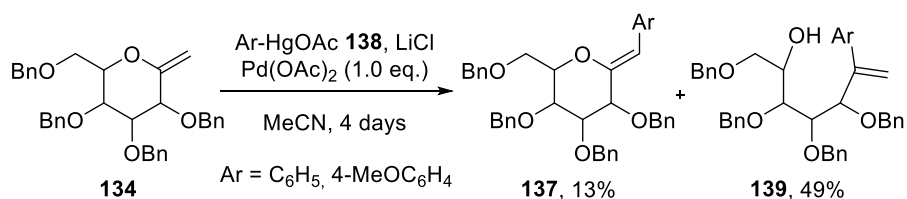
**Figure 10:** Desilylated side-product **136**.

With the methylene *exo*-glycals **133-135** in hands, we moved on to the borylation step. While the olefin metathesis has been widely studied, it has been applied to substrates only vaguely similar to our *exo*-glycals. On the other hand, the Heck reaction was recently exemplified with sugar substrates, and a boryl-Heck reaction has been newly reported, sparking our interest.

### 3.2. The boryl-Heck reaction

#### 3.2.1. Reported work of Bolshan *et al.* and Watson *et al.*

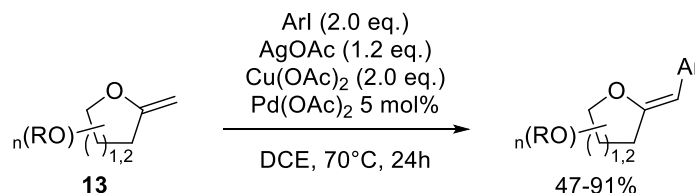
Originally, the preparation of aryl-*exo*-glycals **137** was demonstrated using palladium-catalyzed coupling of *exo*-glycals with organomercurates **138**.<sup>[26]</sup> However, the reaction required a stoichiometric amount of Pd(OAc)<sub>2</sub> and a toxic organometallic partner (**Scheme 51**). Moreover, β-heteroatom elimination was observed to yield the open-chain product **139** as the major product.



**Scheme 51:** Arylation of *exo*-glycal by Reddy and RajanBabu.

More recently, Bolshan and his team reported a new method for the arylation of *exo*-glycals free of organomercurates.<sup>[129]</sup> Extensive optimization work of the catalytic system allowed for the direct coupling of iodoaryls (**Scheme 52**). A wide array of iodobenzene derivatives was used in combination with five and six membered-ring methylene *exo*-glycals **13**.

Triethylsilyl (TES), acetate and benzyl protecting groups were tolerated. Fifty compounds were obtained in a stereoselective manner to afford Z-isomers in average to excellent yields.



**Scheme 52:** Bolshan's Heck coupling of methylene *exo*-glycals.

In parallel to this work focused on the *exo*-glycal substrate, a borylating version of the Heck coupling was disclosed by Watson *et al.* (see chapter 1.2.2.3., page 33).

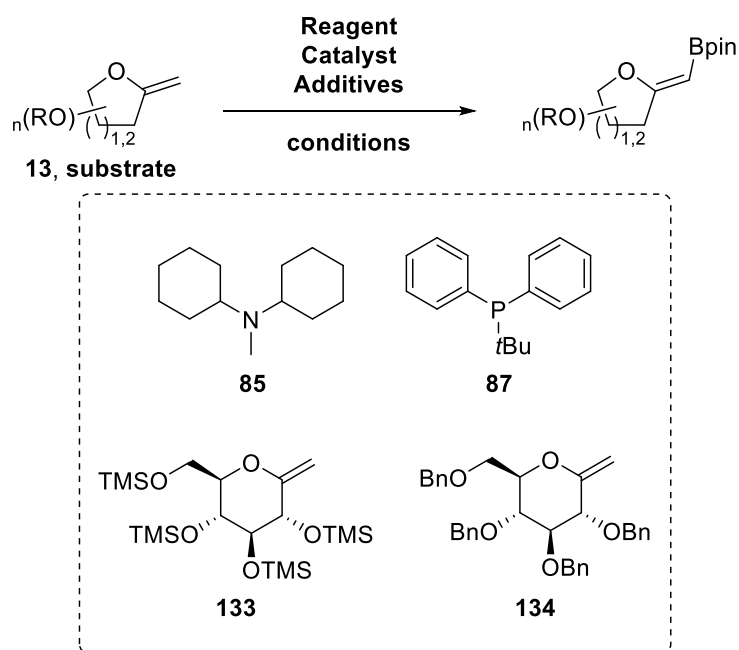
### 3.2.2. Results and discussion

Inspired by Watson's and Bolshan's work, we sought to combine their strategies: the borylation from Watson with the *exo*-glycals substrates from Bolshan. However, the suitable catalytic system and the appropriate reaction conditions needed to be identified. The methylene *exo*-glycals were synthesized (*vide supra*), while the BrBcat was purchased. To replicate Bolshan's catalytic system, the commercially available phosphine **87** was used, despite its suboptimal yields. If promising results were obtained with this phosphine, efforts would be made to obtain phosphine **86**.

Our first preoccupation was to reproduce Bolshan's experiment to validate his conditions. The methylene *exo*-glycal **133** (6-membered ring, TMS protecting groups) reacted with phenyl bromide to yield to corresponding aryl substituted alkene (**Table 1, Entry 1**). The conversion, however, was low. In his publication, Bolshan and his group used iodobenzene derivatives, whereas we used a bromide in anticipation of our boron reagent. The lower reactivity of a brominated compound compared to the one of phenyl iodide could justify the observed conversion. Nevertheless, the desired product was observed, and we moved on to apply those conditions in a boryl-Heck reaction.



**Table 1:** Exploration of the Boryl-Heck reaction.



| Entry          | Substrates | Reagent                         | Additives                      | Conditions                               | Results                               |
|----------------|------------|---------------------------------|--------------------------------|------------------------------------------|---------------------------------------|
| 1 <sup>a</sup> | <b>133</b> | PhBr                            | AgOAc,<br>Cu(OAc) <sub>2</sub> | DCE, 70°C,<br>24h                        | 46%<br>conversion <sup>c</sup>        |
| 2 <sup>a</sup> | <b>133</b> | BrBcat                          | AgOAc,<br>Cu(OAc) <sub>2</sub> | DCE, 70°C,<br>24h,<br>then pinacol<br>1h | Unidentified<br>open chain<br>product |
| 3 <sup>a</sup> | <b>134</b> | BrBcat                          | AgOAc,<br>Cu(OAc) <sub>2</sub> | DCE, 70°C,<br>24h                        | Degradation                           |
| 4 <sup>a</sup> | <b>134</b> | B <sub>2</sub> pin <sub>2</sub> | AgOAc,<br>Cu(OAc) <sub>2</sub> | DCE, 70°C,<br>24h                        | Starting<br>material                  |
| 5 <sup>a</sup> | styrene    | BrBcat                          | AgOAc,<br>Cu(OAc) <sub>2</sub> | toluene,<br>70°C, 24h                    | Degradation                           |

| Entry          | Substrates | Reagent | Additives                      | Conditions                       | Results              |
|----------------|------------|---------|--------------------------------|----------------------------------|----------------------|
| 6 <sup>a</sup> | styrene    | BrBcat  | AgOAc,<br>Cu(OAc) <sub>2</sub> | PhCF <sub>3</sub> , 70°C,<br>24h | Degradation          |
| 7 <sup>b</sup> | <b>134</b> | BrBcat  | <b>85, 87</b>                  | DCE, 70°C,<br>24h                | Starting<br>material |
| 8 <sup>b</sup> | styrene    | BrBcat  | <b>85, 87</b> ,<br>LiI         | toluene,<br>70°C, 24h            | Degradation          |
| 9 <sup>b</sup> | styrene    | BrBcat  | <b>85, 87</b> ,<br>LiI         | PhCF <sub>3</sub> , 70°C,<br>24h | Degradation          |

*a. Reaction carried out using Pd(OAc)<sub>2</sub> as a catalyst; b. reaction carried out using PdCl<sub>2</sub> as a catalyst; c. conversion = product/(reagent+product) estimated by <sup>1</sup>H NMR*

The reaction between methylene *exo*-glycal **133** and BrBcat (**Table 1, Entry 2**) was carried out under the same reaction conditions as Bolshan's experiment, *i.e.* DCE at 70°C for 24 hours. Pinacol is then added to perform a transesterification of the borylated product, to facilitate its purification by chromatography. The <sup>1</sup>H NMR of the crude mixture showed signals consistent with a carbon chain<sup>i</sup>. This seems to indicate the formation of an unidentified open chain product. No traces of **133** were detected, nor were the TMS protecting group signals, indicating the complete desilylation of the compound. A pinacolboronate signal was observed, although with an integration too low to belong to the open chain product. The <sup>11</sup>B NMR spectra of the crude was recorded, showing a small signal at 22.69 ppm that could match the reported signal for BpinOH (22.7 ppm).<sup>[132]</sup> To simplify future NMR analysis, the transesterification step will be omitted.

Given the observation of desilylation, the next reactions were carried out using **134** (6-membered ring, benzyl protecting groups) as the substrate (**Table 1, Entry 3**). No significant signals were observed, except

<sup>i</sup> <sup>1</sup>H NMR (300 MHz, Chloroform-d) δ 7.26 (dd, *J* = 9.8, 4.7 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 4.98 (dd, *J* = 4.7, 4.7 Hz, 1H), 3.99 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.72 (d, *J* = 6.8 Hz, 1H).

the characteristic singlet of benzyl alcohol at 4.70 ppm, suggesting the degradation of the substrate. Changing the less reactive boron reagent for  $B_2pin_2$  only resulted in the recovery of the starting materials (**Table 1, Entry 4**).

The feasibility of a borylated version of Bolshan's Heck reaction was tested using styrene. In order to dissolve this alkene, toluene was chosen as a solvent (**Table 1, Entry 5**). The reaction failed, with only degradation being observed. A similar result was obtained when the solvent was replaced by  $PhCF_3$  to mimic the higher polarity of DCE (**Table 1, Entry 6**).

Since our experiments seem to indicate the incompatibility between Bolshan's catalytic system and a borylating reagent, we turned our attention to Watson's conditions (**Table 1, Entry 7**). The precatalyst palladium(II) chloride was dissolved in DCE, along with the BrBcat, then the phosphine ligand **87** and the amine base **85** were added. A white smoke evolution was observed upon addition of the amine, which could indicate a reaction between the amine and the BrBcat. Lastly, **134** (6-membered ring, benzyl protecting groups) was added and the reaction was stirred for 24 hours at 70°C. After a filtration through celite, the DCE is evaporated and the crude is dissolved in diethyl ether, which cause a precipitate to form. An  $^1H$  NMR analysis of the solid revealed that it consisted of catechol, and signals similar to those of the amine **85**, with the addition of a broad singlet at 10.52 ppm. Considering this spectrum, and the low solubility in diethyl ether, we postulated the formation of an ammonium **140**, with either the bromide from BrBcat or a chloride from the palladium catalyst as a counter-anion (**Figure 11**). The fraction of the crude that dissolved in diethyl ether was analyzed also and consisted of the starting material.

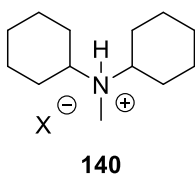


**Figure 11:** Postulated ammonium halide side-product.

We decided to test our reaction conditions with the borylation of styrene. Once again, the solvent was switched for toluene due to the low

solubility of the alkene in DCE (**Table 1, Entry 8**). Lil was also added to prevent the polymerization of the starting olefin. However, only degradation was observed. The more polar PhCF<sub>3</sub> was then used (**Table 1, Entry 9**), but again, no desired product was obtained, and the NMR analysis revealed the presence of ammonium **140**.

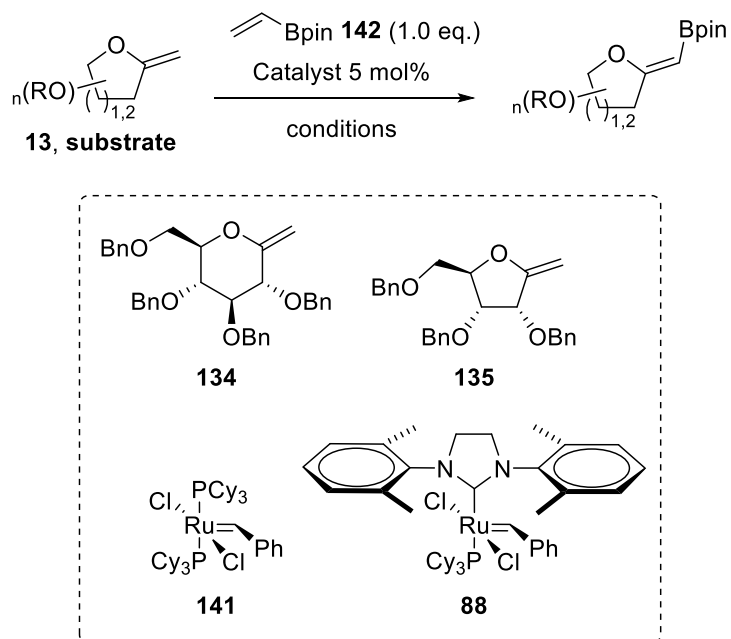
Unfortunately, all our boryl-Heck reaction attempts were unsuccessful. Bolshan's catalytic system, verified with phenyl bromide, was found to be inert with B<sub>2</sub>pin<sub>2</sub>, and led only to degradation when using BrBcat. Similarly, Watson's system did not yield better results. The postulated formation of an ammonium and the observed gas evolution when the reaction is set up hint at the degradation of the BrBcat. This reagent is highly moisture-sensitive. This issue was acknowledged by Watson *et al.*, although they indicate that the reaction can be run in benchtop conditions using standard Schlenk technique, without the need of a glovebox. It is possible though that the amine **85** contains traces of water that hydrolyzed the BrBcat, thereby quenching the desired reactivity.

### 3.3. The olefin metathesis

The background regarding olefin metathesis was covered in the introduction of this thesis (see chapter 1.2.2.4, page 35). The synthesis of borylated alkenes has been reported using both Grubbs I (**141**) and Grubbs II (**88**) catalysts.<sup>[111-113, 115]</sup> The latter showed compatibility with enol ether-type carbon-carbon double bonds, which is why, even if the first generation catalyst was tested, we focused our attention on the second generation catalyst. Grubbs II catalyst has also proven successful with benzyl protecting groups. For this reason, benzyl protected methylene *exo*-glycols **134** and **135** were considered over the TMS-protected **133** in our study. The pinacol vinylboronates **142** was selected as the reaction partner.

The reported reaction conditions for olefin metathesis alter widely. Reflux is often used, though not systematically. The reaction durations commonly found range between 1 hour and one day. We opted for overnight reactions at the boiling temperature of the chosen solvent (**Table 2**). The nature of the solvent was also an important consideration.

**Table 2:** Olefin metathesis using methylene exo-glycols.



| Entry | Substrates           | Catalyst            | Conditions         | Results                                      |
|-------|----------------------|---------------------|--------------------|----------------------------------------------|
| 1     | <b>134</b> (1.0 eq.) | Grubbs I <b>141</b> | DCM, 40°C, 16h     | Starting material + diborylalkene <b>143</b> |
| 2     | <b>134</b> (1.0 eq.) | Grubbs II <b>88</b> | benzene, 80°C, 16h | Starting material + diborylalkene <b>143</b> |
| 3     | <b>134</b> (1.0 eq.) | Grubbs II <b>88</b> | DCM, 40°C, 16h     | Starting material + diborylalkene <b>143</b> |
| 4     | <b>134</b> (5.2 eq.) | Grubbs II <b>88</b> | benzene, 80°C, 16h | Starting material + vinylboronate <b>142</b> |
| 5     | <b>135</b> (4.9 eq.) | Grubbs II <b>88</b> | benzene, 80°C, 16h | Starting material + vinylboronate <b>142</b> |

The Grubbs I catalyst is in most cases used in DCM, therefore it is the solvent we chose for our attempt with this catalyst (**Table 2, Entry 1**). The starting material, methylene exo-glycol **134**, was recovered, and a new

product **143** was formed, identified as the homocoupling of the vinylboronate (**Figure 12**). This phenomenon is a known drawback for this reaction: in addition to the desired cross-metathesis between the reaction partners, both olefins can also undergo homocoupling.

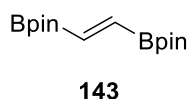


**Figure 12:** Molecule formed by the metathesis of two vinylboronates **142**.

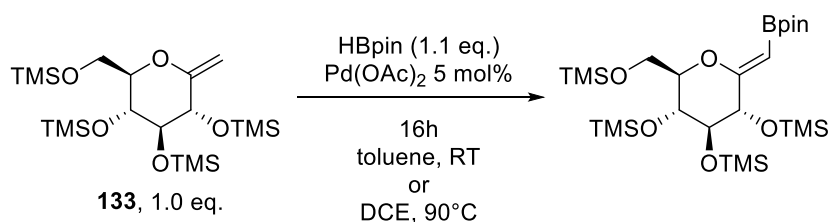
The solvent used in combination with a Grubbs II catalyst vary from the very apolar benzene or toluene to the more polar options such as acetonitrile or DCM. The most promising examples (see **Scheme 36**, c) were carried out in benzene, which is why we selected this solvent for our first attempt (**Table 2, Entry 2**). The crude mixture was composed of the starting material **134**, and the diborylalkene **143**. The reaction was repeated in DCM to judge the impact of the polarity of the solvent, with the same results (**Table 2, Entry 3**).

A frequent answer to the homocoupling of one of the partners is to use a large excess of the other olefin, in our case the methylene *exo*-glycols. Considering the amount of work necessary to obtain these substrates (compare to the commercially available pinacol vinylboronate), this approach is less than ideal and limits the number of potential experiments. This forced us to restrict ourselves to one solvent. Considering that both solvents tested led to the same crude mixture, we continued our work with benzene. Despite its well-known toxicity, benzene was the solvent used for the reported conversion of enol ether,<sup>[115]</sup> and its higher boiling point allows for a more efficient thermal activation compared to DCM. The use of 5.2 equivalents of **134** efficiently discourages the formation of the homocoupling product **143** (**Table 2, Entry 4**). However, this did not bolster the conversion of the starting alkenes, and both **134** and **142** are recovered. The five-membered ring benzyl protected methylene *exo*-glycal **135** was also used in a 4.9 equivalent excess (**Table 2, Entry 5**). In sugar chemistry, the ring size is a known factor influencing the reactivity, but in this instance, it had no impact on the outcome of the reaction.

The synthesis of borylated *exo*-glycals *via* an olefin metathesis reaction was so far unsuccessful. Neither the Grubbs I nor the Grubbs II catalysts were able to promote the borylation of our methylene substrates. While the formation of a diborylalkene demonstrates the potency of these catalysts and their ability to transfer a borylated moiety, our methylene *exo*-glycals remained inert under those reaction conditions. This issue was not addressed as we ran out of time for additional attempts.

### 3.4. Borylation *via* C-H activation

Some work related to the C-H activation of enol ethers followed by a borylation using HBpin has been reported in patents (see chapter 1.2.2.3, **Scheme 31**, page 33).<sup>[100]</sup> The enol ether substrate used in those cases was the simple ethyl vinyl ether. The reaction was conducted under neat conditions, the 4.0 equivalents excess of substrate being able to dissolve the palladium catalyst. However, our methylene *exo*-glycals are solid, so any attempt to replicate this work would require the addition of a solvent (**Scheme 53**).



**Scheme 53:** Borylation of methylene *exo*-glycal *via* C-H activation.

Our first attempt was carried out in toluene at room temperature. The starting *exo*-glycal **133** was recovered, with no signs of degradation or desilylation observed. A more polar solvent was also tested, and given the lack of reactivity of our methylene *exo*-glycal **133**, we decided to perform the reaction at high temperatures. Thus, DCE was selected as a solvent owing to its higher boiling point compare to DCM. The reaction only led to the degradation of the starting material.

None of the boryl-Heck, olefin metathesis or C-H activation reactions showed encouraging results. In consequence, we decided to

abandon the borylation of methylene *exo*-glycols and shift our focus to the direct olefination of sugar lactones instead.

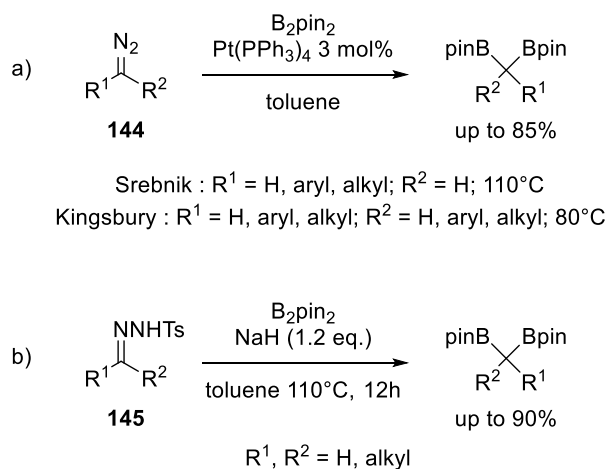


## 4. The boron-Wittig reaction

### 4.1. The *gem*-bisborylalkane reagent

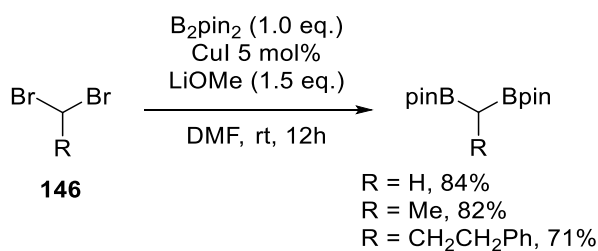
The general principles of the boron-Wittig reaction were covered previously (see chapter 1.2.2.5, page 37). To initiate our own work on the boron-Wittig reaction, a reliable synthesis for the borylalkane reagent is essential. More specifically, and considering our objective to synthesize borylated olefins, our reagent must bear two boron groups attached to the central carbon atom: one boron group to be sacrificed in the process, the other will remain on the final alkene. The synthetic methods to obtain such a *gem*-bisborylalkane are numerous and were the topic of two independent reviews in 2018.<sup>[133]</sup> Herein we present the three most commonly encountered reactions recently used to prepare *gem*-bisborylalkanes, as adopted by different research groups.

The platinum-catalyzed diborylation of diazo compounds **144** to synthesize geminal bis(boron) compounds was originally reported by Srebnik and co-workers.<sup>[134]</sup> However, only a limited range of diazo compounds were tolerated and the reaction temperature was relatively high. The group of Kingsbury extended this method to the diborylation of non-stabilized diazo compounds under milder reaction conditions (**Scheme 54, a**).<sup>[135]</sup> Later on, Wang *et al.* developed a convenient transition metal-free method for synthesizing *gem*-bisborylalkanes using easily prepared N-tosylhydrazones **145** as diazo compound precursors (**Scheme 54, b**).<sup>[136]</sup>



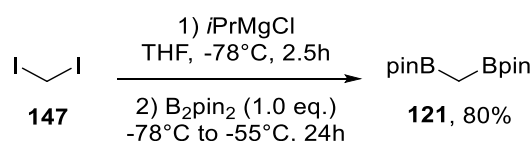
**Scheme 54:** Diborylation of diazo compounds by Srebnik, Kingsbury, and Wang.

Ito's group reported the copper-catalyzed borylation of bromoalkanes with bis-(pinacolato)diboron ( $\text{B}_2\text{pin}_2$ ) as the boron source.<sup>[137]</sup> Among their examples is the transformation of a geminal dibromide (**146**,  $\text{R} = \text{Me}$ ) into the corresponding *gem*-diborylalkane. Later, Marder *et al.* expanded the scope of this reaction, successfully synthesizing both bis[(pinacolato)boryl]methane ( $\text{R} = \text{H}$ ) and alkyl-substituted geminal bis(boron) compounds in moderate to good yields (**Scheme 55**).<sup>[138]</sup> Despite these advancements, the limited commercial availability of substituted geminal dibromides **146** restricts their practicability for the synthesis of geminal bis(boron) compounds. It is noteworthy that the use of air- and moisture-sensitive lithium methyllate requires to work in a glovebox.



**Scheme 55:** Diborylation of *gem*-dibromides by Marder *et al.*

A similar procedure based on diiodomethane **147** was reported by Meek *et al.* (Scheme 56).<sup>[139]</sup> A commercially available Grignard reagent activates the diiodomethane prior to the borylation, while maintaining a low temperature. This protocol, however, has been only applied to unsubstituted diiodomethane. The reaction's temperature, precisely maintained at  $-55^{\circ}\text{C}$  for 24 hours, poses additional challenges, as such temperatures typically require a cryobath rather than standard cooling baths for effective replication.



**Scheme 56:** Diborylation of diiodomethane by Meek *et al.*

The *gem*-bisborylmethane **121** will be the backbone of our chemistry. Therefore, the selection of an adequate synthetic method is critical. For initial investigations, we will use an unsubstituted borylated alkane, so the possibility to synthesize a substituted product is a non-factor. Should the need for a functionalized *gem*-bisborylmethane arise, such compounds can be accessed through a deprotonation/substitution sequence starting from **121** (see Table 7, page 96).

Considering the substantial quantity of reaction that will be carried out using **121**, its synthesis must be scalable. In consequence, the reaction based on hazardous diazocompounds was excluded from consideration. The diazomethane **148** necessary for the preparation of unsubstituted product **121** is an explosive gas, its N-tosylhydrazone **149** equivalent does not exist, and the safer alternative trimethylsilyldiazomethane **150** is too costly for multigram synthesis (Figure 13).

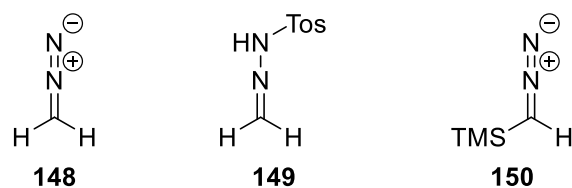
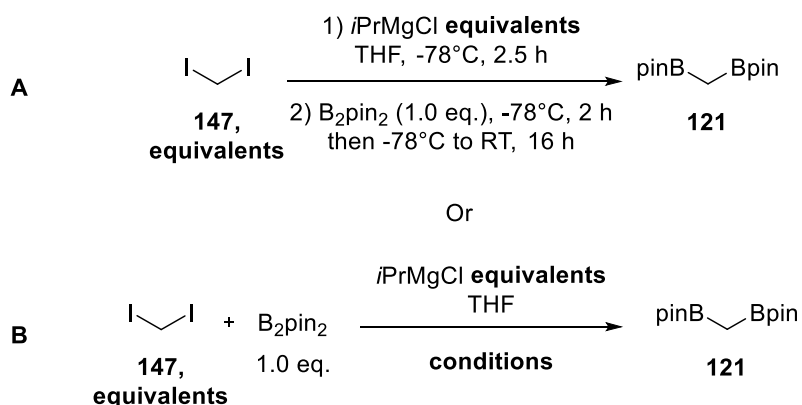


**Figure 13:** Reagents required to obtain **121** via a diborylation of diazo compounds.

Both strategies based on the diborylation of dihalogenoalkanes have been demonstrated on a multigram scale. Although Meek's conditions would be difficult to replicate without a cryobath, the need of a glovebox in Marder's protocol was deemed to be even more tedious for routine work. Thus, we focused our attention on the diborylation of diiodomethane **147** using  $\text{B}_2\text{pin}_2$  and a Grignard reagent (**Table 3**).

**Table 3:** Optimization of the synthesis of **121** on a 100 mg scale.



| Entry | Eq. <b>147</b> | Eq. $i\text{PrMgCl}$ | Conditions | Results <sup>a</sup>          |
|-------|----------------|----------------------|------------|-------------------------------|
| 1     | 4.9            | 4.1                  | <b>A</b>   | 39% conversion                |
| 2     | 4.1            | 4.9                  | <b>A</b>   | 85% conversion,<br>9% yield   |
| 3     | 4.1            | 6.2                  | <b>A</b>   | >99% conversion,<br>34% yield |

| Entry          | Eq. 147 | Eq. <i>i</i> PrMgCl | Conditions                                        | Results <sup>a</sup> |
|----------------|---------|---------------------|---------------------------------------------------|----------------------|
| 4              | 4.2     | 8.6                 | <b>A</b>                                          | No desired product   |
| 5 <sup>b</sup> | 4.2     | 6.4                 | <b>A</b>                                          | 50% conversion       |
| 6 <sup>c</sup> | 4.2     | 6.4                 | <b>A</b>                                          | 26% conversion       |
| 7 <sup>d</sup> | 4.2     | 6.4                 | <b>A</b>                                          | Impurities           |
| 8              | 4.2     | 6.4                 | <b>B</b> -78°C, 4.5h,<br>then -78°C to<br>RT, 16h | 91% conversion       |
| 9              | 4.2     | 6.4                 | <b>B</b> -78°C, 2h,<br>then -78°C to<br>RT, 3h    | 96% conversion       |
| 10             | 4.2     | 6.4                 | <b>B</b> -78°C to RT,<br>16h                      | 97% conversion       |

*a. Conversion =  $1 - B_2pin_2/(121+B_2pin_2)$  estimated by  $^1H$  NMR; b. borylation carried out during 24h instead of 16h; c. reaction carried out in Et<sub>2</sub>O; d. reaction carried out in toluene.*

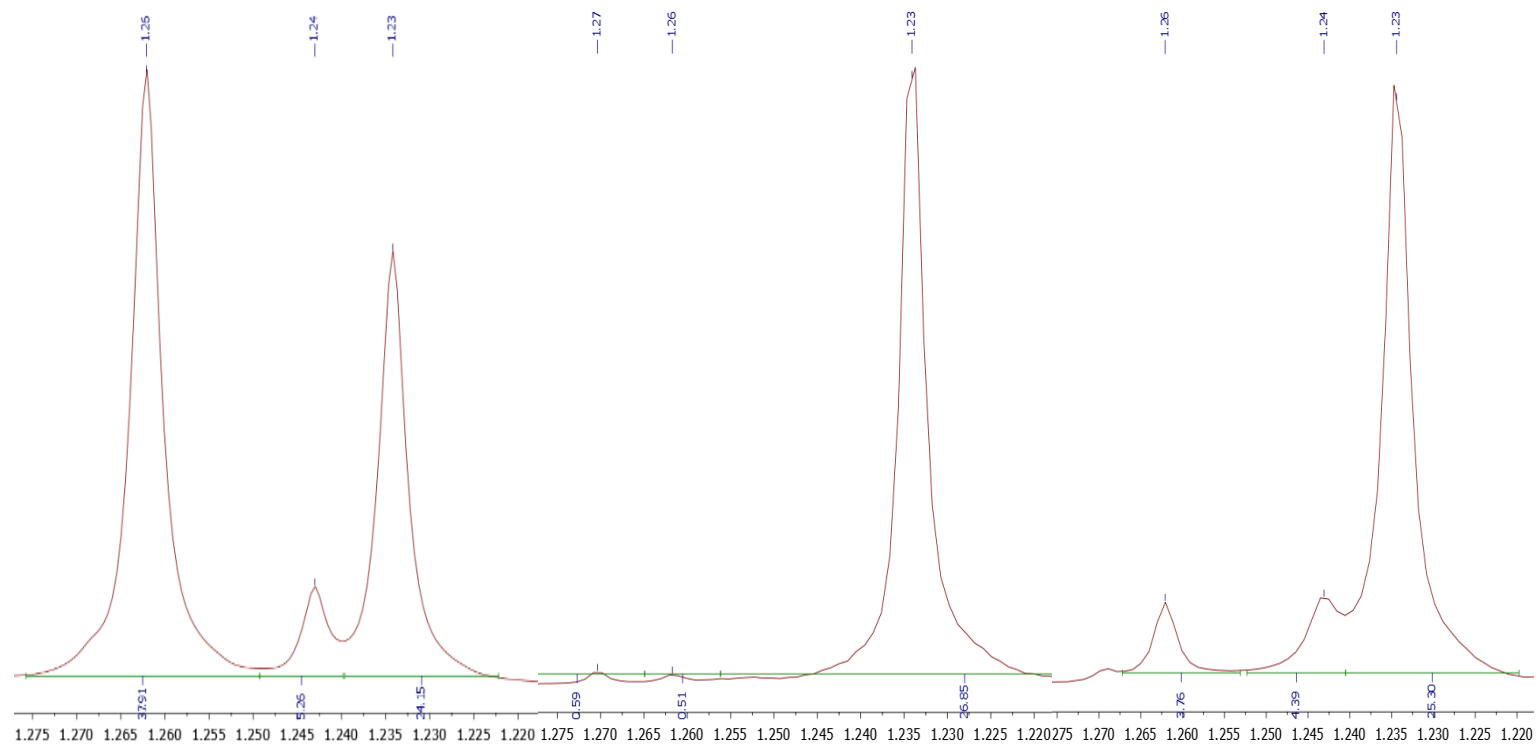
In the absence of a cryobath, adjustments to the reaction conditions were necessary. The first step was kept as is, then the B<sub>2</sub>pin<sub>2</sub> was added at -78°C. This temperature was maintained for two hours, before allowing the reaction to gradually warm up to room temperature overnight, with the cooling bath still in place.

A discrepancy exists in the protocol described by Meek *et al.* in their supporting information section. While the reaction scheme specifies the need of 4.1 equivalents of diiodomethane and 4.9 equivalents of the Grignard reagent, the quantities indicated in the protocol were inverted. We tested first the proportion from the written protocol, 4.9 equivalents of diiodomethane **147** and 4.1 equivalents of *isopropyl* Grignard (**Table 3, Entry 1**). A low conversion of the B<sub>2</sub>pin<sub>2</sub> into the desired *gem*-bisborylmethane **121** is observed. The ratio was then reversed, leading to a

far superior conversion of 85%, while diiodomethane remnant is still observed (**Table 3, Entry 2**). That crude was purified by flash chromatography, with a disappointing 9% yield of the pure product. This accounts for the difficulty to separate **121** from the other impurities, including the B<sub>2</sub>pin<sub>2</sub>. Compounds bearing a Bpin group are known to linger on the silica during a column chromatography or a TLC, due to interactions with the stationary phase.<sup>[140]</sup> In order to facilitate the purification, the consumption of the B<sub>2</sub>pin<sub>2</sub> must be maximized, while the formation of Bpin side-products should be avoided as much as possible.

Seeing that an excess of Grignard is beneficial for the formation of the desired product, the equivalents of Grignard reagent were increased once more. Based on the amount of diiodomethane leftovers in the crude, we chose to use 6.2 equivalent of *i*PrMgCl (**Table 3, Entry 3**). This adjustment eliminated any trace of **147** and left only minor amounts of B<sub>2</sub>pin<sub>2</sub>. A filtration through a silica plug allowed us to remove all of the remaining B<sub>2</sub>pin<sub>2</sub>, but was unsuccessful at separating other impurities.

A comment must be made on those impurities. As they are each characterized by a single singlet in <sup>1</sup>H NMR, their nature couldn't be determined. These singlets, around ~1.25 ppm, are distinctive of a Bpin moiety (**Figure 14**). Each Bpin containing 12 protons, even slight amount of compound would result in a visible signal, even more if the compound bears two Bpin groups (integrating for 24 protons). If these impurities are described by additional signals, they might appear too small to be seen in comparison.



1.26 ppm =  $\text{B}_2\text{pin}_2$ ; 1.23 ppm =  $\text{CH}_2(\text{Bpin})_2$  **121**; 1.24 and 1.27 ppm = Bpin impurities.

**Figure 14:**  $^1\text{H}$  NMR (300 MHz, Chloroform-*d*) spectra for **Entry 1** (top left), **Entry 2** (top right) and **Entry 3** (bottom).

To consume the last traces of B<sub>2</sub>pin<sub>2</sub>, the amount of **147** was slightly increased. Considering the positive impact that a larger amount of Grignard had in **Entry 3**, we pushed it further with 8.6 equivalents (**Table 3, Entry 4**). The NMR analysis of the crude mixture reveals a combination of B<sub>2</sub>pin<sub>2</sub> and other impurities. The principal signal is a singlet at 1.23 ppm, typical of the desired *gem*-bisborylmethane, but the protons of the central carbon of **121** (usually found at 0.35 ppm) are not present. Therefore, the reaction failed to produce the desired *gem*-bisborylmethane, and the main compound, observed at 1.23 ppm, is a new impurity.

Since an increased amount of Grignard reagent was detrimental for the reaction, the reaction was carried out over a day to convert the remaining B<sub>2</sub>pin<sub>2</sub>, instead of the usual sixteen hours (**Table 3, Entry 5**). Surprisingly, the ratio between the B<sub>2</sub>pin<sub>2</sub> and the desired CH<sub>2</sub>(Bpin)<sub>2</sub> worsen.

We also experimented with alternative solvents. The use of diethyl ether (**Table 3, Entry 6**) led to a poor conversion of the starting B<sub>2</sub>pin<sub>2</sub>, and the 1.23 ppm impurity, which signal superimposes to the one of the desired product **121**, is observed. When the reaction was carried out in toluene, all of the B<sub>2</sub>pin<sub>2</sub> was consumed, but the desired product is only minor in the crude mixture (**Table 3, Entry 7**). The foremost substances observed are the 1.23 ppm and 1.24 ppm impurities.

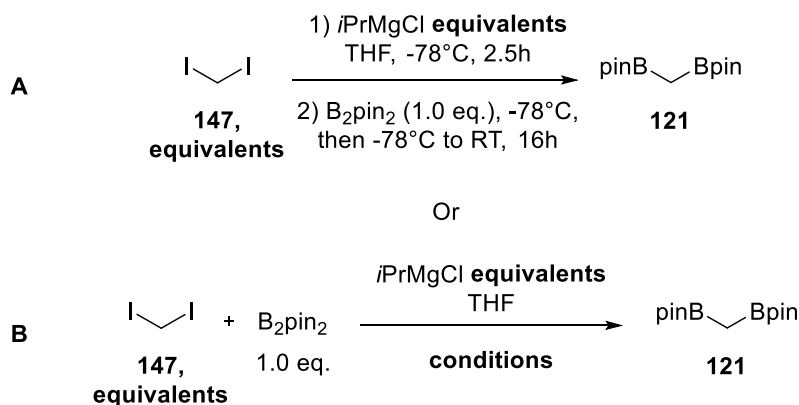
We were also interested in the possibility of carrying out the reaction in a one-step “Barbier-like” procedure **B**. Here, the B<sub>2</sub>pin<sub>2</sub> was dissolved in dry THF alongside the diiodomethane **147**, before the Grignard reagent is added. We started exploring this possibility on a 100 mg scale, with a low temperature maintained during four and a half hours, before a slow warm up of the mixture during the night (**Table 3, Entry 8**). A satisfying, although incomplete, conversion of the borylated reagent was observed, with traces of some impurities. We then shortened the reaction time, which led to a slightly better conversion (**Table 3, Entry 9**). A similar result was obtained when the reaction was simplified to an overnight procedure (**Table 3, Entry 10**).

Among all attempts, the conditions from **Entry 3** proved to be the most effective. None of our efforts to further improve conversion of B<sub>2</sub>pin<sub>2</sub> or to reduce the amount of borylated sideproducts bore fruits. All of the



reactions of **Table 3** were carried out on a 100 mg scale (based on the initial B<sub>2</sub>pin<sub>2</sub> input); our next goal was the scaling up of the reaction (**Table 4**).

**Table 4:** Optimization of the synthesis of **121** on a multi-gram scale.



| Entry          | Scale  | Conditions                                  | Results <sup>a</sup>      |
|----------------|--------|---------------------------------------------|---------------------------|
| 1              | 300 mg | <b>A</b>                                    | 36% conversion            |
| 2              | 300 mg | <b>B</b> -78°C, 2h,<br>then -78°C to RT, 3h | 92% conversion            |
| 3              | 300 mg | <b>B</b> -78°C to RT, 16h                   | 98% conversion            |
| 4              | 900 mg | <b>B</b> -78°C to RT, 16h                   | 92% conversion, 32% yield |
| 5              | 2.7 g  | <b>B</b> -78°C to RT, 16h                   | 88% conversion, 30% yield |
| 6 <sup>b</sup> | 2.7 g  | <b>B</b> -78°C to RT, 16h                   | 98% conversion, 62% yield |

*a. Conversion = 1 – B<sub>2</sub>pin<sub>2</sub>/(**121**+B<sub>2</sub>pin<sub>2</sub>) estimated by <sup>1</sup>H NMR; b. reaction carried out using 4.6 equivalents of **147** and 5.2 equivalents of *i*PrMgCl.*

We began with a three-fold increase of the reaction scale (from 100 mg to 300 mg) following the conditions developed previously (**Table 4, Entry 1**). To our dismay, the conversion dropped significantly, and numerous borylated impurities were observed. After repeating the reaction twice, we estimated an average conversion of 36% across the three attempts.

Once again the one-step procedure was tested, but this time on a tripled reaction scale. The five hours protocol (**Table 4, Entry 5**) as well as the overnight version (**Table 4, Entry 6**) efficiently converted the starting 300 mg of B<sub>2</sub>pin<sub>2</sub>, outperforming the two-step procedure **A**. Encouraged by these results, we continued to progressively scale-up the reaction to 900 milligrams of B<sub>2</sub>pin<sub>2</sub> (**Table 4, Entry 7**), then to 2.7 grams (**Table 4, Entry 8**), using the overnight one-step procedure. However, as the scale increased, the conversion of the starting material gradually declined. In consequence, the subsequent purifications were also more complicated, with pure yields stagnating at around 30%.

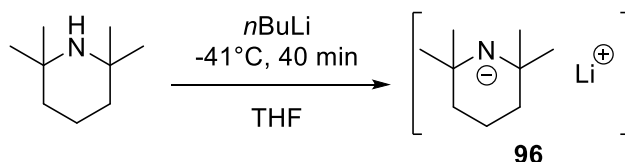
Taking into consideration the detrimental impact of unreacted B<sub>2</sub>pin<sub>2</sub> on the purification step, we decided to further tweak the ratio of reagents. The new equivalents allow for a better conversion of the B<sub>2</sub>pin<sub>2</sub> by forming more sideproducts (**Table 4, Entry 8**). These sideproducts, as well as the excess diiodomethane, were easier to separate from the desired product. Only the 1.23 ppm impurity, mentioned above, exhibited a retention factor (rf) close to the one of product **121**, and must be eluted carefully. This revised protocol was the first to lead to the preparation of a significant amount of product, in a good yield of 62%.

Although a lot of time and efforts were dedicated to this optimization, it ended up being a success. While the yield is not as high as the one reported by Meek *et al.*,<sup>[139]</sup> we developed a simplified version of their protocol. Our “Barbier-like” one-step overnight reaction allows the synthesis of the desired product on a multi-gram scale without the need for a cryobath. More than 27 g of the *gem*-bisborylmethane **121** were prepared during this thesis, with yields ranging from 56% to 79%, depending on the effectiveness of the flash chromatography. The amount of product synthesized, combined with its central place in this chapter, justify the investment in this optimization process.

#### 4.2. The boron-Wittig reaction of lactones

The *gem*-diborylalkane **121** was subsequently used to explore the boron-Wittig reaction of lactones. As a starting point for our researches, we chose to adapt a procedure from Grygorenko *et al.* which involves the *in situ* generation of lithium tetramethylpiperidine (LiTMP) **96** at -30°C during

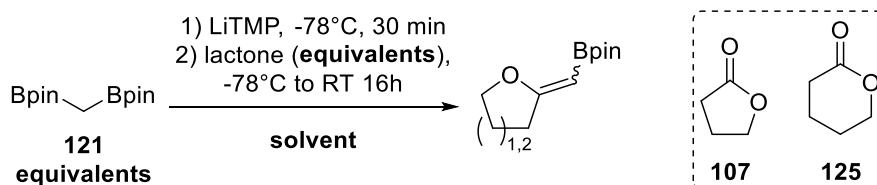
30 min.<sup>[141]</sup> It is unclear as to how they reached this temperature, as it is not available through commonly used cooling bath. We decided to generate our LiTMP, by deprotonation of tetramethylpiperidine using *n*-buthyl lithium, at -41°C (acetonitrile/dry ice bath) and to compensate this lower temperature by extending the duration to 40 minutes (**Scheme 57**).



**Scheme 57:** *In situ* generation of LiTMP.

To this THF solution of LiTMP is added the *gem*-bisborylmethane **121** at -78°C. A ratio of 1.2 equivalents of LiTMP for every equivalent of bisborylmethane is maintained throughout this whole thesis. Both the  $\delta$ -valerolactone **125** and  $\gamma$ -butyrolactone **107** were then used as model substrates for the boron-Wittig reaction. Some of our results on the screening of reaction conditions are reported in **Table 5**.

**Table 5:** Exploration of the boron-Wittig reaction with lactones.



| Entry          | Solvent           | CH <sub>2</sub> (Bpin) <sub>2</sub><br>(eq) | Lactone<br>(eq) | Conversion <sup>a</sup> | Results                                  |
|----------------|-------------------|---------------------------------------------|-----------------|-------------------------|------------------------------------------|
| 1 <sup>b</sup> | THF               | 1.0                                         | 1.3             | full                    | <b>151</b>                               |
| 2 <sup>b</sup> | THF               | 2.0                                         | 1.0             | full                    | <b>151</b> (min.) +<br><b>152</b> (maj.) |
| 3 <sup>b</sup> | Et <sub>2</sub> O | 1.0                                         | 1.3             | full                    | <b>151</b> (maj.) +<br><b>152</b> (min.) |
| 4 <sup>b</sup> | Toluene           | 1.0                                         | 1.3             | full                    | <b>151</b>                               |

| Entry           | Solvent           | CH <sub>2</sub> (Bpin) <sub>2</sub><br>(eq) | Lactone<br>(eq) | Conversion <sup>a</sup> | Results                                     |
|-----------------|-------------------|---------------------------------------------|-----------------|-------------------------|---------------------------------------------|
| 5 <sup>b</sup>  | Anisole           | 1.0                                         | 1.3             | full                    | <b>151</b> (maj.) + <b>152</b> (min.)       |
| 6 <sup>c</sup>  | THF               | 1.0                                         | 1.1             | no                      | <b>121</b> + <b>107</b>                     |
| 7 <sup>c</sup>  | THF               | 1.0                                         | 5.5             | full                    | <b>153</b>                                  |
| 8 <sup>c</sup>  | THF               | 2.0                                         | 1.0             | partial                 | <b>121</b> + <b>107</b> + <b>154</b> (min.) |
| 9 <sup>c</sup>  | Et <sub>2</sub> O | 1.0                                         | 1.2             | partial                 | <b>121</b> + <b>107</b> + <b>153</b> (min.) |
| 10 <sup>c</sup> | Toluene           | 1.0                                         | 1.2             | no                      | <b>121</b> + <b>107</b>                     |
| 11 <sup>c</sup> | Anisole           | 1.0                                         | 1.2             | full                    | <b>153</b>                                  |

*a: Conversion of the starting lactone as estimated by <sup>1</sup>H NMR on the crude mixture; b. reaction using **125** as the substrate; c. reaction using **107** as the substrate.*

The reaction carried out in THF (**Table 5, Entry 1**) and toluene (**Table 5, Entry 4**) with an excess of  $\delta$ -valerolactone **125** gave the same crude mixture. No traces of the starting lactone were observed, but signals corresponding to a carbon chain could be found in the <sup>1</sup>H NMR of the crude mixture. 1D NMR experiments indicates a five carbons chain with a carbonyl on one end, and alcohol on the other; and HMBC presented a correlation between the two extremities, making it a cyclic compound. Although this data aligns with  $\delta$ -valerolactone's structure, the chemical shifts of the observed signals were upfielded (**Figure 15**). To confirm that the new structure **151** was distinct from the starting material, pure **125** was added to the NMR tube of **151**, leading to two distinctive sets of signals.

When the solvent is switched to Et<sub>2</sub>O (**Table 5, Entry 3**) or anisole (**Table 5, Entry 5**), the unidentified lactone **151** is observed, as well as a methylated product **152** (**Figure 15**). The formation of this side-product will

be discussed later (*vide infra*). Notably, the starting material **125** was not observed by NMR.

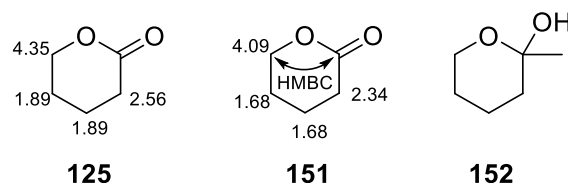


**Figure 15:**  $^1\text{H}$  NMR shifts of lactone **125** and unknown product **151**, methylated product **152**.

Taking a bit of distance with Grygorenko's procedure, we used the boron reagent in a two equivalents excess (**Table 5, Entry 2**). The resulting crude mixture showed the absence of lactone **125**, while unidentified compound **151** and methylated side-product **152** could be found. A small signal matching the analytical expectations ( $^1\text{H}$  NMR) for a proton geminal to the boryl group of an alkenylboronate was also detected.

A similar set of reaction was performed in parallel on  $\gamma$ -butyrolactone **107**. No conversion of the starting lactone occurred when THF (**Table 5, Entry 6**) or toluene (**Table 5, Entry 10**) were used as solvent, both of the starting material **121** and **107** were recovered at the end of the reactions. A new unidentified product **153** was obtained when the reaction was carried out in Et<sub>2</sub>O (**Table 5, Entry 11**), in anisole (**Table 5, Entry 9**), or with a large excess of lactone (**Table 5, Entry 7**). NMR analyses indicate the presence of a ketone in an open chain **153** (**Figure 16**). The right extremity of the chain presents a signal at 1.58 ppm in  $^1\text{H}$  NMR, which would require the presence of a shielding functional group such as a boronate group. While this theory is supported by the presence of Bpin signals in the  $^1\text{H}$  NMR spectrum, those signals could belong to residual **121**. Furthermore, the amount of product obtained after purification was too low to perform a  $^{11}\text{B}$  NMR.

The only boron-Wittig reaction with **125** showing signs of a product matching the expected signals of a borylated *exo*-glycal was using an excess of *gem*-bisborylmethane **121**. The same conditions were applied to lactone **107**. A crude mixture constituted of both reactants was obtained, with the presence of a new methylated product **154** (**Figure 16**). Once more, a small

signal that could correspond to an alkenylboronate was observed, at 5.36 ppm. Unfortunately, only a few milligrams of this compound could be isolated, rendering the unambiguous identification difficult (the  $^{11}\text{B}$  NMR and  $^{13}\text{C}$  NMR were inconclusives).

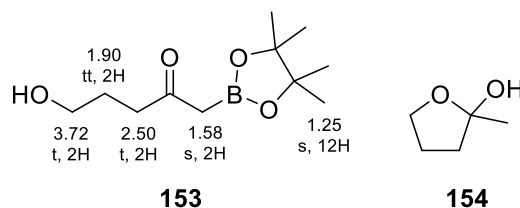
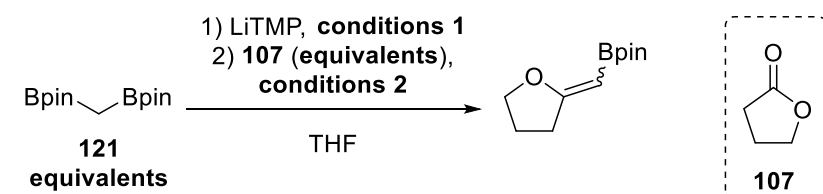


**Figure 16:**  $^1\text{H}$  NMR shifts of unknown product **153**, and methylated product **154**.

In most cases, the formation of many side-products was observed resulting in complex crude mixtures. However, a potential boron-Wittig product could be observed when an excess of *gem*-bisborylamethane was used, although only in a minute amount. The  $\delta$ -valerolactone **125** was fully converted regardless of the nature of the solvent used and the reactant proportions, leading to difficult NMR analyses. Accordingly, we continue our work with the less reactive  $\gamma$ -butyrolactone **107**. We tried to reproduce the experiment in **Table 5, Entry 8**, however, much to our surprise, all our numerous attempts using the exact same procedure were unsuccessful (only the starting materials being recovered).

We decided to further explore our reaction conditions to optimize the formation of the product of interest. Building on the conditions described in **Table 5, Entry 8** as our working base, several modifications were tested (**Table 6**).

**Table 6:** Optimization of the boron-Wittig reaction between **121** and **107**.



| Entry | CH <sub>2</sub> (Bpin) <sub>2</sub><br>(eq.) | Conditions 1                  | Conditions 2                     | Results                       |
|-------|----------------------------------------------|-------------------------------|----------------------------------|-------------------------------|
| 1     | 3.0                                          | -78°C, 30 min                 | -78°C to RT, 16h                 | <b>121 + 107</b>              |
| 2     | 1.5                                          | -78°C, 30 min                 | -78°C to RT, 16h                 | <b>121 + 107 + 153</b> (min.) |
| 3     | 2.0                                          | -78°C, 30 min                 | -78°C to RT, 48h                 | <b>121 + 107</b>              |
| 4     | 2.0                                          | -78°C, 30 min                 | -78°C to RT, 3h                  | <b>121 + 107</b>              |
| 5     | 2.0                                          | 0°C, 10 min                   | 0°C, 10 min,<br>then RT, 16h     | <b>121 + 107</b>              |
| 6     | 2.0                                          | -78°C, 30 min                 | -78°C to RT, 1h<br>then 80°C, 3h | <b>107</b>                    |
| 7     | 2.0                                          | -78°C, 30 min<br>TMEDA 1 eq.  | -78°C to RT, 16h                 | <b>121 + 107</b>              |
| 8     | 2.0                                          | -78°C, 30 min<br>DABCO, 1 eq. | -78°C to RT, 16h                 | <b>121 + 107</b>              |

Considering that our most encouraging result so far was obtained using a two-equivalents excess of *gem*-bisborylmethane **121**, we continued exploring that parameter. The amount of borylated reagent was increased to three equivalents, but only the starting materials were recovered, without any visible traces of the interesting 5.36 ppm signal (**Table 6, Entry 1**). Since a larger excess of **121** had a negative impact on the reactivity, a smaller excess of 1.5 equivalents was tested (**Table 6, Entry 2**). Apart from

the reagents, the only noteworthy signals present in the crude mixture were traces of compound **153**, already observed previously (**Table 5, Entry 7, 9 and 11**).

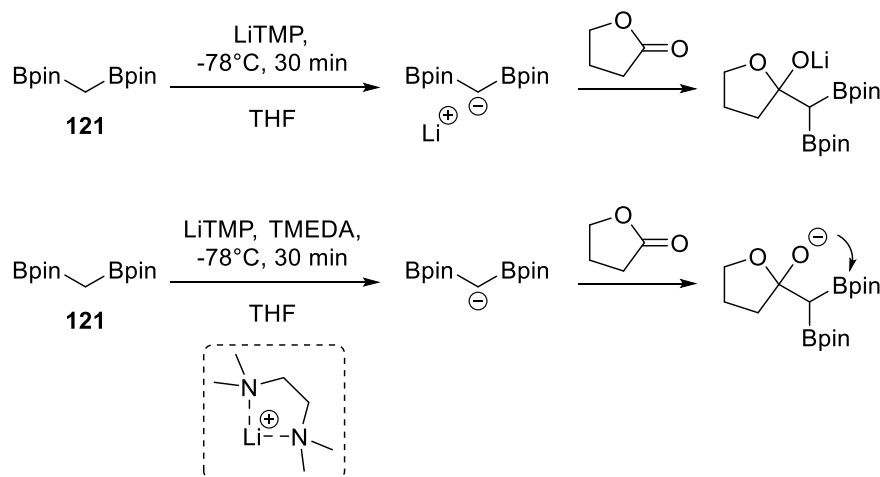
As it would seem that only a strict two-to-one excess of *gem*-bisborylmethane **121** in regard of lactone **107** could lead to the formation of the potential boron-Wittig product, other strategies were put in motion to boost the reactivity. The duration of the reaction was lengthened to two days, leading only to the recovery of some of the reagent, and a partial degradation (**Table 6, Entry 3**). It is possible that the desired vinylboronate product is formed, then degraded in the reaction medium. A shorter reaction time was tested, but no significant signals were observed except these of the starting materials (**Table 6, Entry 4**).

An alternative approach to favor the conversion of the reagent would be to raise the temperature during the reaction, which would furnish more energy to overcome eventual activation barriers. However, given the use of organolithium species in our medium, we proceeded with caution. We began by carrying out the deprotonation and addition steps at 0°C, without noticing any variation of the crude mixture's composition (**Table 6, Entry 5**). Next, we attempted to reflux the reaction (**Table 6, Entry 6**). For this, we first carried out the reaction at -78°C, giving an hour for the organolithium species to react, then heating up the reaction to facilitate the remaining steps of the boron-Wittig reaction. Only traces of the lactone **107** were observed, alongside some signal characteristic of Bpin moieties. The protons on the central carbon of **121** were not detected, suggesting the complete degradation of the *gem*-bisborylmethane.

The use of a nucleophilicity enhancer, such as TMEDA, was reported on some occasions to improve the reactivity *gem*-bisborylmethane anion.<sup>[142]</sup> These compounds would act as a lithium scavenger, dissociating the ion pair and hence increasing the nucleophilicity of the anion (**Scheme 58**). The boron-Wittig reaction was carried out in the presence of TMEDA, with no noticeable improvement (**Table 6, Entry 7**). Only traces of the 5.36 ppm signal were observed on the <sup>1</sup>H NMR spectra, alongside both the lactone and the borylated reagent. We replicated the procedure with a different nucleophilicity enhancer, DABCO, without more success (**Table 6,**



**Entry 8).** The trapping of lithium cation will be further discussed later (see **Table 23**, page 169).



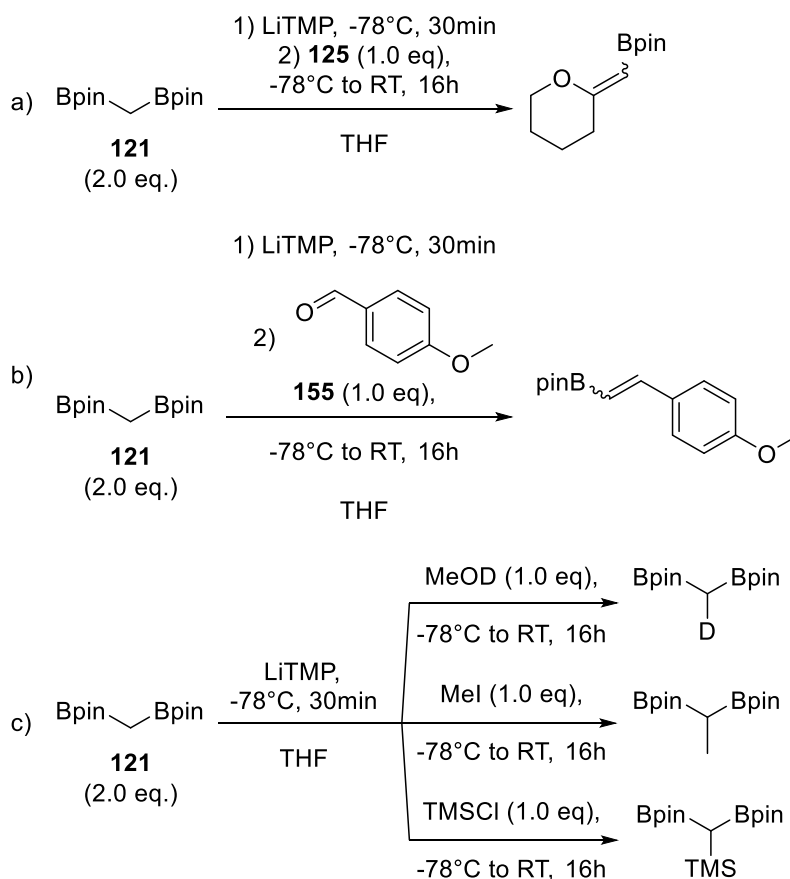
**Scheme 58:** Action of the nucleophilicity enhancers in the boron-Wittig mechanism.

Despite our varied strategies to favor the conversion of the starting materials **121** and **107** and the formation of a potential borylated *exo*-glycal product (like the one symbolized by its 5.36 ppm signal in  $^1\text{H}$  NMR spectra), none proved successful. The reaction conditions described in **Table 5**, **Entry 8** couldn't be surpassed. Since the synthesis of the 5.36 ppm compound couldn't be improved through chemical efforts, we decided to run the reaction on a one-gram scale, hoping to obtain enough material, after purification by flash chromatography, to conduct more thorough analyses. Unfortunately, this last ditched effort failed also.

During our work on the reaction conditions outlined in **Table 6**, we observed an unexpected general decline in reactivity. In most cases, the crude mixture was mainly constituted of the borylated reagent and small amount of lactone (mostly lost in aqueous work-up due to water solubility). The  $^1\text{H}$  NMR spectra, however, were never clean, the baseline was systematically covered by a series of small but numerous impurities signals. After a few months of work, the general aspect of the spectra changed. It would appear as if the NMR analysis was run on a simple physical mixture

of **121** and **107** instead of the result of a complex procedure involving very reactive organolithium species.

We designed a set of experiments to confirm this reactivity issue, and to pinpoint its origin (**Scheme 59**).



**Scheme 59:** Reactivity test of the *gem*-bisborylmethane anion.

The  $\delta$ -valerolactone **125** was demonstrated to be more reactive than the  $\gamma$ -butyrolactone **107**. We decided to replicate our conditions described in **Table 5, Entry 2 (Scheme 59, a)**. Neither of the side-products **151** or **152** were observed. Instead, a very clean mixture of the borylated reagent **121** and the lactone **125** appeared in the  $^1\text{H}$  NMR spectra. The complete lack of conversion of **125** confirmed the drop of reactivity witnessed earlier, and its independence towards the lactone's nature. The

borylation of *p*-anisaldehyde **155**, which was previously reported *via* a boron-Wittig reaction,<sup>[141]</sup> was also unsuccessful (**Scheme 59**, b). Once again, the starting materials were recovered in a clean mixture.

To demonstrate the efficiency of our deprotonation procedure of **121**, the hypothetically formed *gem*-bisborylmethane anion was used in substitution reactions. The nucleophilic attack on deuterated methanol, iodomethane, or trimethylsilyl chloride should have led respectively to a deuterated, methylated, or silylated *gem*-bisborylalkane (**Scheme 59**, c). Yet, none of the aforementioned products were detected.

Our reflection on this phenomenon led us to realize that the decreased reactivity coincided with the inauguration of a dry solvent dispenser in our research facility. Since then, the reactions were carried out in the THF provided by this machine, while bottled dry THF had been previously used. To prove that the recently observed reactivity drop was connected to the source of THF, a reaction in anisole was replicated. The composition of the crude mixture was identical to the one obtained previously (**Table 5**, **Entry 11**), including signals for the unidentified compound **153**.

The borylation of *p*-anisaldehyde (**Scheme 59**, b) was carried out again in parallel reactions using THF originating either from a bottle or the dispenser. While the reaction performed in the THF from the dispenser only led to a clean mixture of the starting reactants, the bottled THF allowed for the partial conversion of the *p*-anisaldehyde to the expected product. An NMR yield of 28% was measured (using DMT as an internal standard), well below the published yield of 62%.<sup>[141]</sup> Nonetheless, this result clearly demonstrated the impact of the solvent's quality. A side-by-side comparisons of the spectra recorded evidenced without a doubt the difference in reactivity between both THF sources (**Figure 17**).

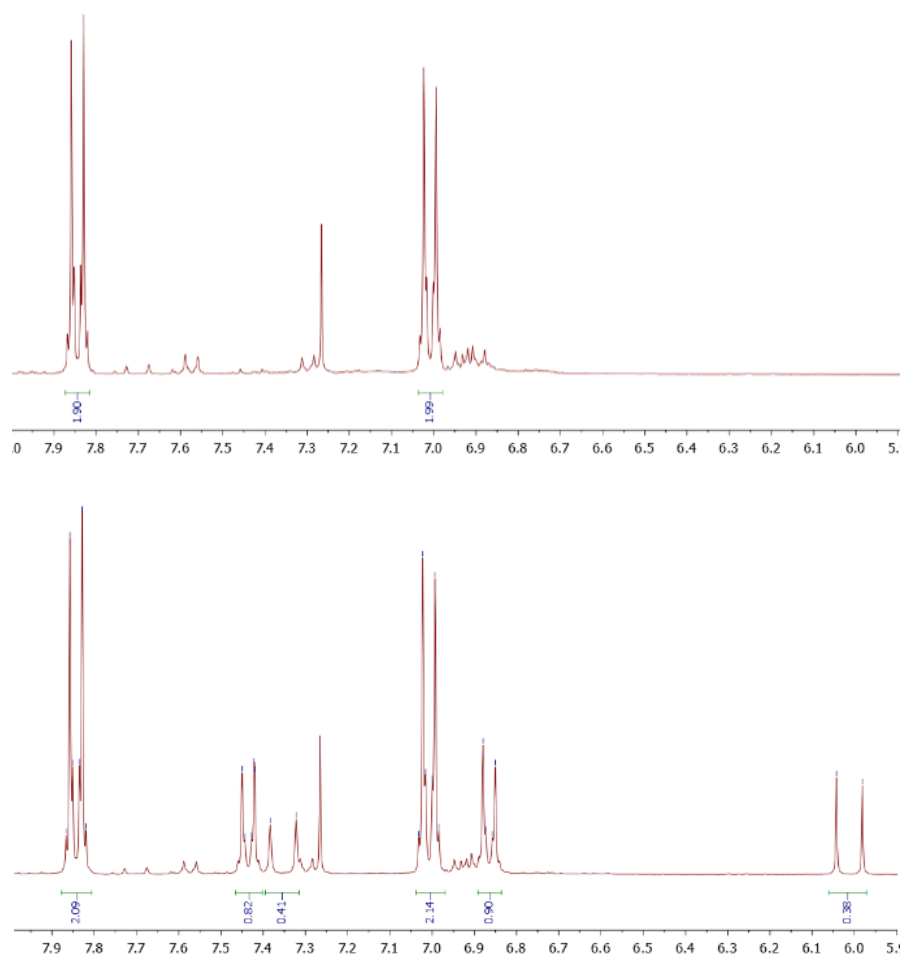


**Figure 17:**  $^1\text{H}$  NMR of the borylation of *p*-anisaldehyde with dispenser (left) and bottle (right) THF.

In consequence, all reactions initially ran in the THF provided by the dispenser were replicated using bottle dry THF. With the exception of the experiments described in **Scheme 59**, all the olefination reactions discussed in this thesis were ultimately conducted with bottle THF.

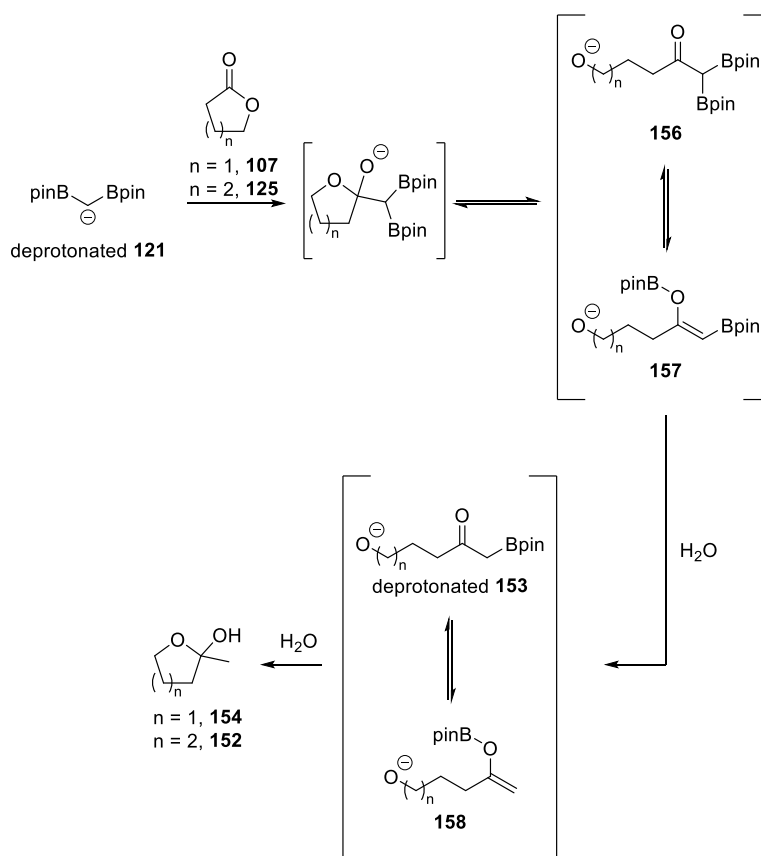
To explain this difference of reactivity between the two sources of THF, we postulated that slight variations in the solvent composition must exist. The bottle THF probably includes an impurity that acts as an activator, even in concentration as low as a few ppm. This impurity, if identified, could potentially serve as catalyst in the boron-Wittig reaction. We

searched for any divergences in the solvents composition, but, unfortunately, very few information were available to us. The butylated hydroxytoluene (BHT), a common stabilizer for ether solvents, was ruled out, as both of the solvent sources claims to be stabilizer-free. Our next guess was the different degree of hydration between the solvents, the dispenser supposedly providing a more anhydrous THF. To verify this assertion, a reaction was carried out using the solvent from the machine, but without flame-drying the glassware beforehand (the argon atmosphere was still upheld). This allowed us to introduce water in the reaction, although in a very slight proportion. Regrettably, the dispenser provided solvent, with a small addition of hydration, didn't yield results approaching those obtained with bottled THF. If anything, it led to more degradation being observed in the  $^1\text{H}$  NMR spectra.

To our disappointment, none of our boron-Wittig reaction conditions led non-ambiguously to the formation of a borylated cyclic enol ether. Traces of an intriguing compound at 5.36 ppm were detected on several occasions, but only a few milligrams of this specie were isolated, leaving its characterization inconclusive. Quite several reaction conditions have been explored, and the most promising one has been identified. An excess of two equivalents of *gem*-bisborylmethane is crucial, and the addition steps must be completed at low temperature, before a slow warm-up to room temperature overnight.

#### 4.3. Lactone and *gem*-bisborylmethane modifications

While the side-product **151** remains unidentified, the formation of proposed compound **153**, as well as the methylated products **152** and **154**, can be rationalized by revisiting the boron-Wittig mechanism (**Scheme 60**).



**Scheme 60:** Mechanism of the boron-Wittig reaction with lactones.

As detailed in **Scheme 43**, the carbanion formed by deprotonating *gem*-bis(boryl)alkane **121** initiates a nucleophilic attack on an ester. This process establishes a rapid equilibrium between the  $\alpha,\alpha$ -bis(boryl)ketone **156** and its borate enol form **157**, arising from the C to O migration of a Bpin group. From this enol form, a first hydrolysis can occur. The resulting  $\alpha$ -borylketone corresponds to the structure we put forward for the side-product **153**, also in equilibrium with its borate enol form **158**. A second hydrolysis step, combined with a ring closure, affords the methylated side-product **154**. A similar mechanism would explain the formation of **152** from the lactone **125**.

These observations provide insights into lactone reactivity. Specifically, lactone ring opening occurs more rapidly than the formation of

a four-member cycle (see **Scheme 37**, page 38). It is from this open form that the hydrolysis of the boron group can proceed. However, the open chain can undergo a subsequent cyclisation as suggested by the formation of a hemiketal such as **154**. Therefore, several strategies were put in motion based on the presumed mechanism of the boron-Wittig reaction with lactones.

#### 4.3.1. Modification of the borylated reagent

First, to discourage the hydrolysis of the intermediate, leading to the loss of the boron groups, a *gem*-bisborylmethane bearing hydrolysis-resistant boryl groups was envisaged. The moisture-stable MIDA boron ester group was ideally suited that role. The synthesis of *gem*-bisborylmethane **159** should be achievable, but such a reagent could prove difficult to deprotonate (**Figure 18**, left). Indeed, the MIDA boronic esters are less electron-deficient than Bpin groups due to the coordination of the nitrogen atom to the boron. Furthermore, and for the same reason, a MIDA boronate would also be less susceptible to the nucleophilic addition of an alcoholate, an essential step in the boron-Wittig process. In consequence, we opted for the non-symmetric *gem*-bisborylmethane **160** (**Figure 18**, right), which combines an electrophilic Bpin group to perform the boron-Wittig reaction, and a BMIDA group to resist the hydrolysis.

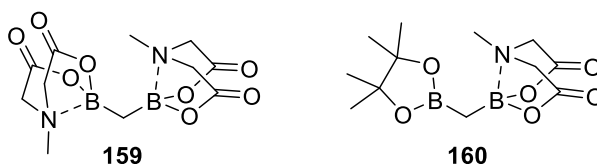
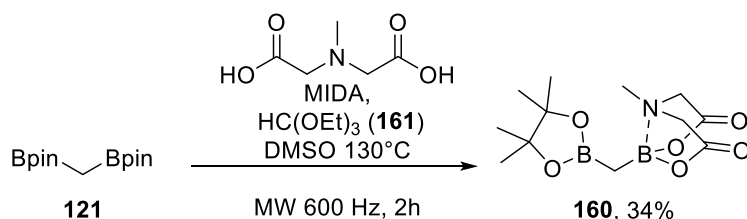


**Figure 18:** *Gem*-bisborylmethanes bearing a moisture-stable BMIDA group.

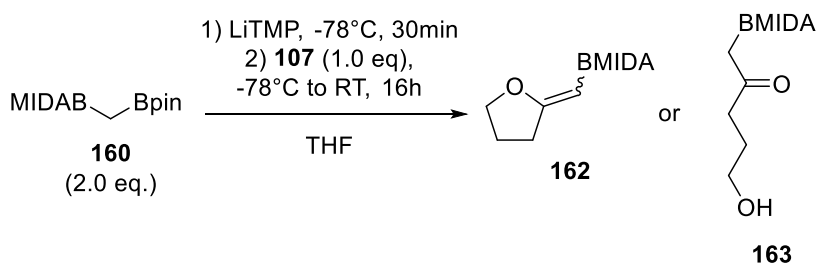
The synthesis of **160** was the result of an adapted protocol from Sharma *et al.* (**Scheme 61**).<sup>[143]</sup> The reaction relies on the selective monotransesterification of *gem*-bisborylmethane **121** using methyliminodiacetic acid (MIDA) in DMSO. The orthoester **161** is used as a homogenous (unlike MgSO<sub>4</sub> or molecular sieve) desiccant agent. The reaction proceeds at high temperatures, and Sharma indicated the need of using thick-walled glassware, which hints that increased pressure may be

involved. As such glassware was unavailable in our lab, we decided to use a microwave reactor, which is equipped with tubes designed to sustain moderate pressures. Additionally, microwave-assisted reactions have been reported to produce a more efficient heating of the reaction mixture, thereby shortening the reaction time.<sup>[144]</sup> We decided to carry out our reaction during two hours, rather than the overnight procedure reported by Sharma *et al.*



**Scheme 61:** Synthesis of the asymmetrical Bpin/BMIDA *gem*-bisborylmethane.

The desired product **160** was obtained in 34% yield, after purification by flash chromatography. While this was a quite modest result, it has to be put in perspective with the reported yield of 40% obtained by Sharma *et al.* after several steps of optimization. They indicated that the starting material **121** can be recovered during the purification, a finding we also confirmed, and used again in a new transesterification reaction. They reported a yield of 72% after three such cycles. In our case, the amount of asymmetrical *gem*-bisboryl methane **160** synthesized was sufficient for the subsequent attempt to use it in a boron-Wittig reaction (**Scheme 62**).

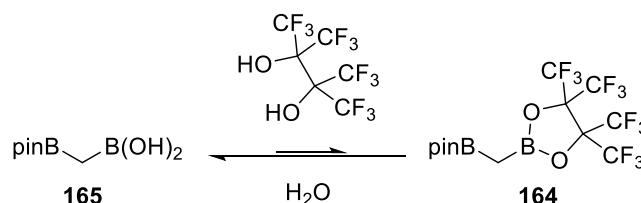


**Scheme 62:** Boron-Wittig reaction on lactone using the Bpin/BMIDA reagent.



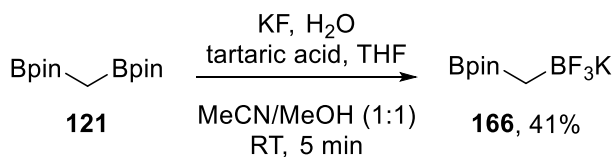
Unfortunately, the desired product **162** is not formed. Instead, reactants **160** and **107** are recovered in a clean mixture, without any traces of the expected side-product **163**, a MIDA analog of **153**. This compound would have resulted from the opening of the lactone followed by the hydrolysis of the Bpin moiety. We concluded that the deprotonation of asymmetrical *gem*-bisboryl methane **160** was inefficient.

In a diametrically opposed strategy, we hypothesized that an enhanced electrophilicity of the boronate group could promote formation of a four membered ring and hence the boron-Wittig reaction. This idea was inspired by Erker's work, illustrated in **Scheme 44**, page 43.<sup>[125]</sup> We endeavor to synthesize compound **164**, bearing a perfluorinated pinacolboronate moiety, designed to enhance the boron's electrophilicity. We expected that the transesterification of boronic acid **165**, despite being favored from an entropic perspective, would be directed toward the hydrolysis (**Scheme 63**) due to the improved electrophilicity imparted by the fluorinated Bpin.



**Scheme 63:** Transesterification of boronic acid using perfluoro pinacol.

Instead, we focused on an esterification strategy based on trifluoroboronate intermediate. This required the preliminary synthesis of asymmetrical *gem*-bisboryl methane **166** bearing a  $\text{BF}_3\text{K}$  moiety. Such a reaction was described by Marsawa *et al.*,<sup>[145]</sup> building on the elegant procedure developed by Lloyd-Jones and co-workers for the fluorination of boronic acids (**Scheme 64**).<sup>[146]</sup> This transformation requires a very precise ratio of solvents to involve all the reaction partners, while provoking the precipitation of inorganic salts that drives the conversion to completion in a matter of minutes. The use of the much more readily handled KF is preferred to the famously glassware-destructive  $\text{KHF}_2$ .<sup>[147]</sup>



**Scheme 64:** Fluorination of *gem*-bisborylmethane **121**.

The reaction was a success, even though it was tainted by a low conversion. The presence of the starting material **121** prompted the need for a purification by recrystallization, leading to a 41% yield. The selectivity towards the monotransesterification was rationalized by the proximity of the borylated groups which allows for a fluorine to partially fill the empty p orbital of the Bpin, diminishing its electrophilicity (**Figure 19**).<sup>[145]</sup>

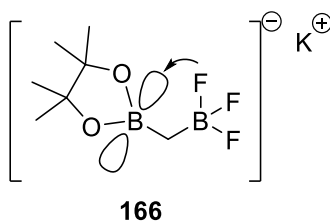
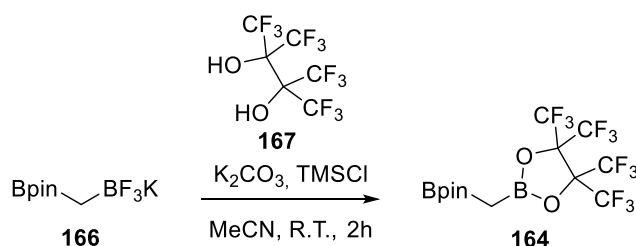


**Figure 19:** Stabilization of the Bpin group by a proximal fluorine atom.

We envisioned a boron-Wittig reaction between **107** and **166**, even if this latter is probably even more complicated to deprotonate than **160**, but the trifluoroborate proved insoluble in THF.

An *in situ* silicon-driven deborylation,<sup>[148]</sup> followed by an esterification with perfluoropinacol **167**, was then carried out in an attempt to synthesize **164** (**Scheme 65**). Regrettably, only degradation was observed. As it is often the case in boron chemistry, the need for a more reactive compound faces the increased instability of said compound, and the challenging synthesis that comes with it.



**Scheme 65:** The combination of a deborylation and the following esterification of **166**.

#### 4.3.2. Modification of the metal cation

As discussed above, to avoid the side-reactions and obtain the boron-Wittig product, one must favor the four membered ring formation *via* the nucleophilic attack of the alkoxy moiety on the boron group, over the ring-opening of the lactone. Since the use of an especially electron-deficient borylated group presented substantial challenges (*vide supra*), we focused instead on increasing the nucleophilicity of the oxygen anion. A common strategy for this purpose is the addition of a nucleophilicity enhancer, an approach that we already experimented without success (see **Table 6, Entries 7-8**, page 77). Another way to achieve this goal is to swap the lithium counter-cation for another metal. Indeed, the impact of the nature of the metallic counter-ion of an alcoholate on the electron-density of the oxygen has been demonstrated.<sup>[149]</sup> A typical strategy would be to replace a strong lithiated base such as LiHMDS by its sodium counterpart NaHMDS. Unfortunately, the hexamethyldisilazide anion was found to be incapable of deprotonating *gem*-bisborylmethane **121**.

Although sodium and potassium alternatives to LiTMP have been reported, they have hardly been utilised. Even if the isolation of NaTMP on a multi-gram scale has been achieved by Hevia *et al.*, an *in situ* transmetallation strategy between LiTMP and sodium or potassium *tert*butoxy should prove more appropriate.<sup>[150]</sup> NaTMP and KTMP have just recently started to be efficiently used for selective deprotonations.<sup>[151]</sup> Their magnesium equivalent, however, has been known for decades. Indeed, Hauser and Walker reported a series of azides with magnesium bromide or chloride as counter-cation, including **167**, **168** and **169** (**Figure 20**).<sup>[152]</sup>

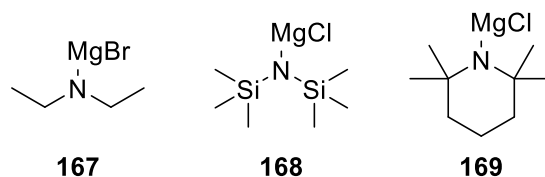
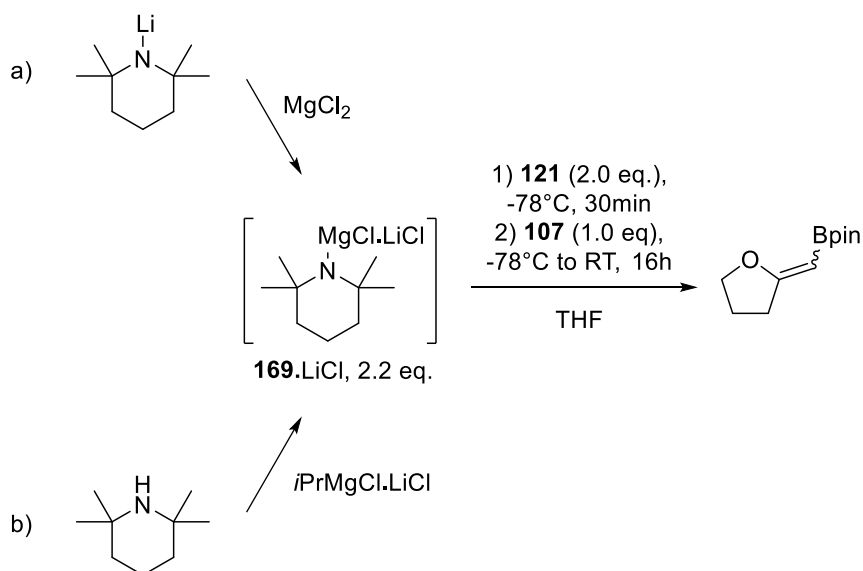


**Figure 20:** Selected example of the Hauser bases.

The application of these bases was impaired by their low solubility in organic solvents and their sluggish reactivity. Knochel *et al.* addressed this issue with the addition of lithium chloride.<sup>[153]</sup> Such compounds were named Knochel-Hauser bases, or sometimes Turbo-Hauser bases, after the Turbo Grignard developed by Knochel a few years earlier.<sup>[154]</sup>

We endeavor to synthesize the Turbo-Hauser base TMPMgCl and use it in a boron-Wittig reaction with a lactone. This should lead to a magnesium alkoxide, more nucleophilic than its lithium counterpart. Two methods are exploited for the synthesis of Turbo-Hauser bases, we decided to try both. The first strategy simply requires the addition of  $\text{MgCl}_2$  to a preformed organolithium (**Scheme 66, a**), while the second is based on the direct metalation of the amine using Turbo Grignard (**Scheme 66, b**).



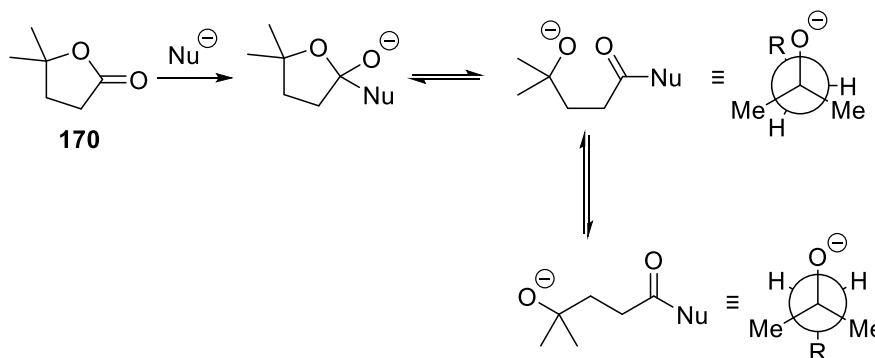
**Scheme 66:** *In situ* generation of a Turbo-Hauser base, and the subsequent boron-Wittig reaction.

These reactions didn't afford the desired borylated enol ether. The lactone **107** was partially recovered, alongside the *gem*-bisborylmethane **121** and some minor degradation products. However, the Turbo-Hauser base being generated *in situ*, its presence in our reaction medium cannot be guaranteed.

#### 4.3.3. Modification of the lactone substrate

The ring opening of the lactone is an issue preventing the formation of the desired cyclic enol ether. Thus, to disfavor this competing side reaction, adequate modifications of the lactone substrate were designed.

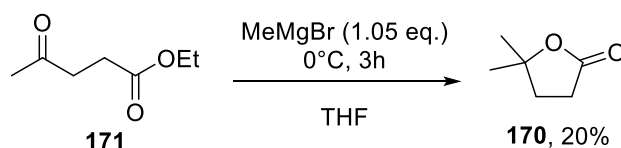
We reasoned that the  $\alpha$ -methylation of a carbon within the lactone skeleton would allow us to benefit from a Thorpe-Ingold effect<sup>[155]</sup> and disfavor the ring-opening of the lactone (or favor the opposite reaction) (**Scheme 67**). Accordingly, dimethylated lactone **170** was considered. While this effect can be gained by the  $\alpha$ -methylation of any of the carbon of the ring, the choice of position in  $\alpha$  of the alcoholate moiety benefits from another effect, this one electronic. The two methyl groups enhance the nucleophilicity of the adjacent oxygen *via* their inductive electron-donating effect, increasing its propensity to maintain the lactone in its cyclic form.



**Scheme 67:** The Thorpe-Ingold effect of dimethylated lactone **170**.

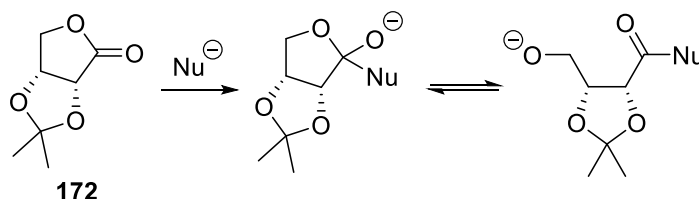
A clever protocol by Ryu *et al.* was followed for the synthesis of dimethylated lactone **170** (**Scheme 68**).<sup>[156]</sup> The Grignard reagent methylates the ketone function of ethyl levulinate **171**, in a two birds one stone step: the necessary quaternary carbon, from which the Thorpe-Ingold

effect arises, is created, while at the same time an alkoxy group is formed. This alcoholate will then perform a transesterification on the ester to obtain a decent amount of a crude mixture mainly constituted of the desired lactone. However, the purification only afforded pure **170** in a 20% yield, a low value compared to the reported 74%. This issue was not further investigated, as enough material was obtained to carry out a boron-Wittig reaction.



**Scheme 68:** Synthesis of dimethylated lactone **170** from ethyl levulinate.

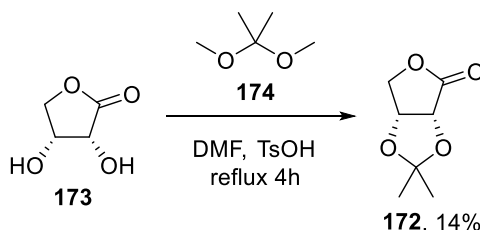
A second modified lactone was prepared in order to suppress the ring opening pathway. The bicyclic compound **172** presents structural constraints, on top of a Thorpe-Ingold effect originating from the substitution of the carbon chain. Should this lactone undergo the ring-opening side-reaction, the second ring will maintain both the alcoholate and the carbonyl moieties in close proximity, encouraging the recyclization (**Scheme 69**). An acetonide was selected to play the role of the second ring as it is a commonly represented protecting group in sugar (and therefore, glycal) chemistry.



**Scheme 69:** Ring-opening of bicyclic lactone **172**.

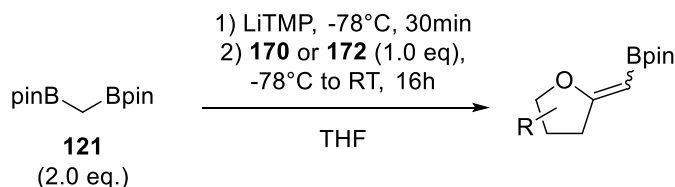
The synthesis of the bicyclic lactone **172** only requires a straightforward protection of the commercially available D-erythrionolactone **173**.<sup>[157]</sup> This was accomplished by reaction with excess 2,2-dimethoxypropane **174** in DMF in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) at reflux for four hours (**Scheme 70**) to afford

**172** in 14% yield after purification by flash chromatography (Piccialli *et al.* reported a yield of 95%). We suspected that the bicyclic lactone **172** is at least partially water-miscible, and that most of it was lost during the work-up. However, since the reaction yielded enough product for a boron-Wittig attempt, further optimization was not pursued.



**Scheme 70:** Synthesis of bicyclic lactone **172** from D-erythrionolactone.

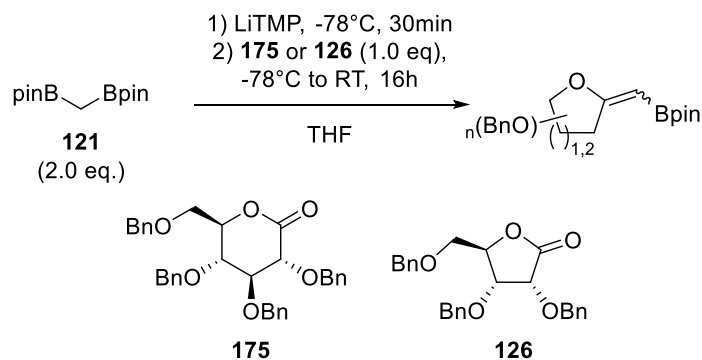
Both lactones **170** and **172** were used in a boron-Wittig reaction with *gem*-bisborylalkane **121** (**Scheme 71**). In the reaction with lactone **170**, we recovered the lactone itself, while the borylated reagent degraded. In the case of bicyclic lactone **172**, the lactone was not found (possibly lost during aqueous work-up), but in this case compound **121** was intact in the crude mixture. In both reactions, traces of the elusive signal at 5.36 ppm were observed.



**Scheme 71:** Boron-Wittig reaction on lactone using the modified lactone.

For good measure, sugar lactone substrates **175** and **126** were also used in a boron-Wittig reaction (**Scheme 72**). While model lactones **107** and **125** allow for a simplified procedure and easier analyses, it is not impossible that the protected hydroxy groups can impact the olefination process. The reaction between **121** and **175** led to the full conversion of the sugar lactone, in part with the previously described reactivity of six-membered ring lactone (see chapter 4.2, **Table 5**, page 74). The analysis of the resulting complex mixture by  $^1\text{H}$  NMR only allowed for the identification of the

starting *gem*-bisborylmethane **121**. When sugar lactone **126** is used instead, it is fully recovered within a clean crude mixture.



**Scheme 72:** Boron-Wittig reaction on benzyl-protected sugar lactone substrates.

Neither the borylated group variations, the swapping of the base's cation, nor the lactone modifications led to any noticeable improvement in the boron-Wittig conversion of lactones. We thus decided to conduct a step-by-step examination of this reaction to identify the key factors responsible for these failures.

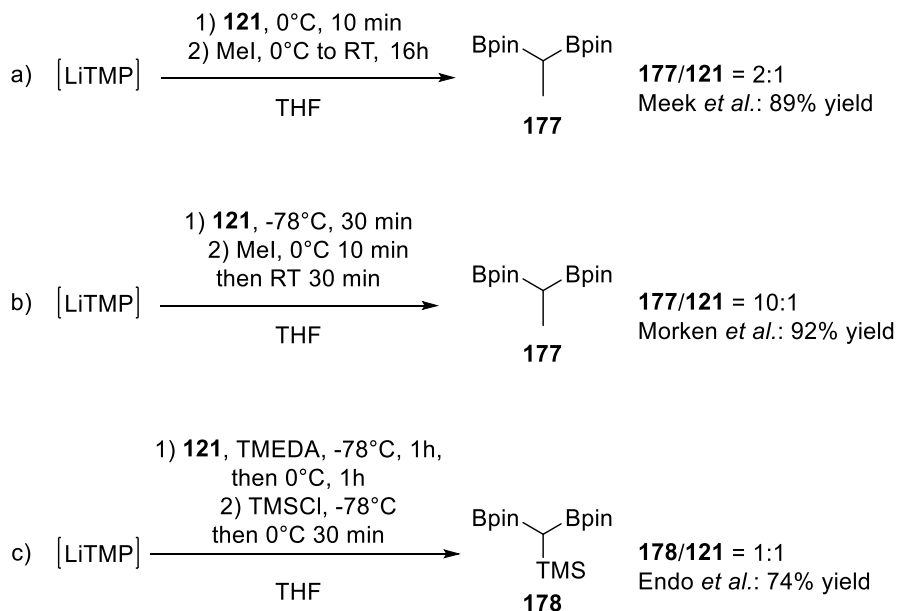
#### 4.4. Experimental mechanistic studies of the boron-Wittig reaction

##### 4.4.1. The deprotonation step

The boron-Wittig reaction starts with the *in situ* formation of the bulky LiTMP base, and the subsequent deprotonation of the borylated reagent, in our work, the *gem*-bisborylmethane **121**. To verify the good conduct of this initial deprotonation, we replicated substitution procedures reported by Meek (**Scheme 73, a**),<sup>[139]</sup> Morken (**Scheme 73, b**),<sup>[158]</sup> and Endo (**Scheme 73, c**),<sup>[159]</sup> all well-established in the field of the boron-Wittig research. The comparison between the three protocols shed a light on the wide variety of reaction conditions reported for such transformation. While the THF is universally chosen as a solvent, the temperatures and durations of the substitution differ broadly, as well as the presence or absence of TMEDA as a nucleophilicity enhancer. Even the origin of the LiTMP solution



is not consistent, as Morken and Meek used solid LiTMP in a glove box, while Endo prepared it *in situ* from tetramethylpiperidine and *n*butyllithium.



**Scheme 73:** Substitution of *gem*-bisborylmethane **121** by Meek, Morken, and Endo.

In this trial, the best product-to-reagent ratio was observed using Morken's conditions. Accordingly, we continued our work with this protocol. As we were more interested in the silylated product **178** (see **Scheme 90**, page 120) than the methylated **177** one, the substitution with TMSCl was further explored (**Table 7**).

**Table 7:** Optimization of **121**'s central carbon substitution.

| <div><div><div><div><div>Bpin</div><div>121, 1.0 eq.</div></div><div><div><div>1) LiTMP (1.2 eq.),<br/>-78°C, 30 min<br/>2) TMSCl, 0°C 10 min<br/>then RT 30 min</div><div>THF</div></div><div><div><div>Bpin</div><div>178</div></div><div><div>TMS</div></div></div></div></div></div></div> |           |                |                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------|-----------------|
| Entry                                                                                                                                                                                                                                                                                          | TMSCl Eq. | Additive       | 178/121         |
| 1                                                                                                                                                                                                                                                                                              | 1.1       | /              | 3/1             |
| 2                                                                                                                                                                                                                                                                                              | 1.5       | /              | 12/1            |
| 3                                                                                                                                                                                                                                                                                              | 1.1       | TMEDA, 1.2 eq. | 18/1            |
| 4                                                                                                                                                                                                                                                                                              | 1.5       | TMEDA, 1.2 eq. | 32/1, 75% yield |

Our first aim was to replicate Morken's work as described, except for the swapping of MeI for TMSCl (**Table 7, Entry 1**). Although the conversion was somewhat lower than in the methylation conditions (**Scheme 73, b**), it still exceeded the one observed under Endo and Shibata's conditions (**Scheme 73, c**). We increased the equivalent of TMSCl to promote further conversion of the starting material, with some success (**Table 7, Entry 2**). In parallel, the effect of adding TMEDA in the reaction medium was studied, resulting in a six-fold increase in the conversion of **121** (**Table 7, Entry 3**). Both modifications were combined, leading to a satisfactory ratio of **178** observed and a 75% yield obtained after purification (**Table 7, Entry 4**).

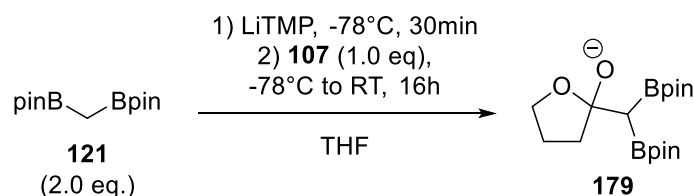
Since Matteson's pioneering work,<sup>[142a]</sup> the use of TMEDA has been omitted by most of the research group working on the boron-Wittig reaction, raising questions about its necessity. It is conceivable that the positive impact of the TMEDA is not, in this instance, linked to the oxygen's nucleophilicity enhancement as a result of its influence on the lithium, but rather to an increase of the polarity of the medium.

This set of experiments demonstrated the effectiveness of the *gem*-bisboryl methane **121** deprotonation by LiTMP, and that the carbanion thus

formed is sufficiently nucleophilic to engage in the compulsory attack in a substitution reaction. This short optimization process provided us with a substitution procedure for the central carbon of **121**, should the need arise, as well as the product **178**, exploited within this thesis.

#### 4.4.2. The addition step

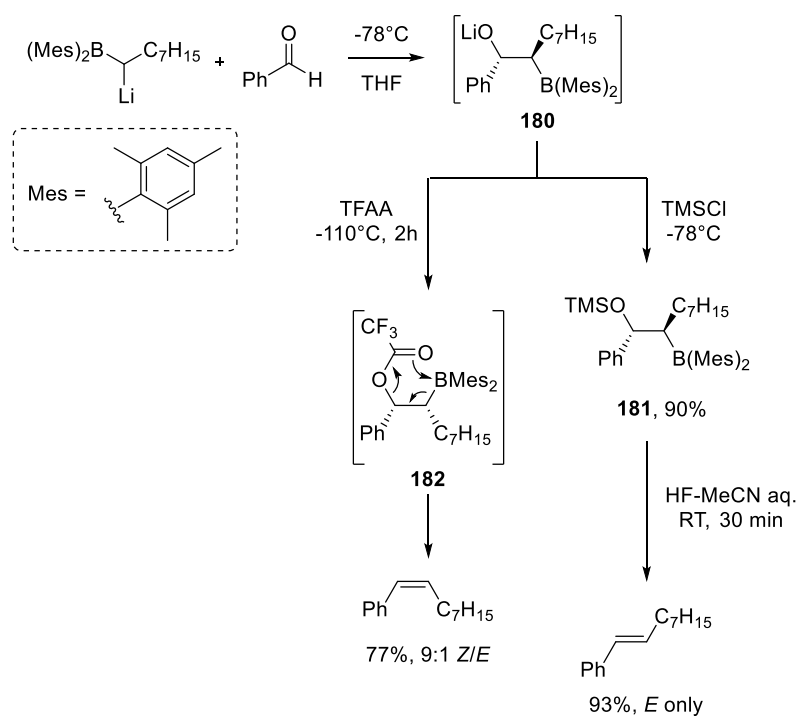
As the carbanion originating from **121** was demonstrated to be nucleophilic enough to perform a substitution reaction, its ability to add to an ester function was next in line in our study. On this matter, we were interested in the trapping of the alkoxide **179** that would result from such an addition (**Scheme 74**).



**Scheme 74:** Addition of deprotonated **121** to an ester, leading to the alkoxide intermediate **179**.

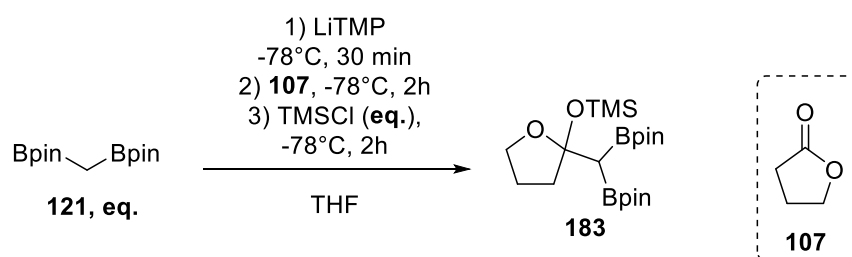
The trapping of intermediate **179** would basically quench the reaction, preventing it to proceed with the boron-Wittig as well as the ring-opening/hydrolysis process. The isolation of a trapped **179** would provide a strong evidence of the sufficient reactivity of our *gem*-bisborylmethane.

In this regard, we took an interest in Pelter's work on a similar topic.<sup>[160]</sup> His team demonstrated the possibility to trap the alkoxide intermediate **180** formed during the stereoselective boron-Wittig reaction between a borane and an aldehyde (**Scheme 75**). The result relied on the nature of the trapping agent. When TMSCl is used, the intermediate **181** was isolated, and the subsequent desilylation/elimination afforded the corresponding *E* olefin. In contrast, the trapping using trifluoroacetic anhydride (TFAA) forced the alkoxide **180** to adopt an eclipsed conformation stabilized by the presence of the ester function in **182**, an intermediate that could not be isolated as it underwent spontaneous elimination.



**Scheme 75:** Pelter's trapping strategies.

While Pelter's work is inspirational, his experimental details were far from exhaustive. Key information regarding the equivalent of the involved partners, as well as clear instructions about the timing for adding the trapping reagent and the appropriate work-up procedure are missing. Nonetheless, using our best judgment, we tried to trap alkoxide **179** with TMSCl (**Table 8**).

**Table 8:** Trapping attempts using TMSCl.

| Entry | 121 eq. | TMSCl eq. | Modification                                    | Yield (%) |
|-------|---------|-----------|-------------------------------------------------|-----------|
| 1     | 1.2     | 1.2       | /                                               | 0         |
| 2     | 2.0     | 1.2       | /                                               | 0         |
| 3     | 2.0     | 2.0       | /                                               | 0         |
| 4     | 2.0     | 2.0       | -78°C to RT, 2h (step 2)<br>RT, 30 min (step 3) | 0         |

In all experiments, the lactone **107** is used in one equivalent, while a 1.2 to 1 ratio is maintained between LiTMP and the *gem*-bisborylmethane **121**. In the absence of precise guidance in Pelter's report, we decided to use our most successful conditions yet (**Table 5, Entry 8**), with TMSCl added last to allow sufficient time for the addition reaction to proceed.

Cautious about the possibility for our borylated carbanion to perform a substitution on TMSCl (as described above), we started our investigation with 1.2 equivalent of both the reagent **121** and the TMSCl (**Table 8, Entry 1**). While the desired product was not observed, we were satisfied that no silylated compound **178** was found. Consequently, we raised the amount of reagent **121** to two equivalents, without meeting more success (**Table 8, Entry 2**). The quantity of TMSCl was increased also, to no avail (**Table 8, Entry 3**).

Although Pelter's sole clear experimental detail is the need of low temperatures, we were concerned this might constitute an obstacle for the reaction to overcome the energetic barrier of the addition step. Therefore, we carried out our addition and trapping steps at higher temperatures

(Table 8, Entry 4). Once again, no traces of the desired product were observed.

In each of these experiments, however, we consistently detected a low signal at 0.22 ppm on the  $^1\text{H}$  NMR spectra. This matches the shift expected for a trimethylsilylether proton, which could correspond to product **184**, resulting from the trapping of the open-chain form of the adduct (Figure 21), or a compound derived from it. Only a few milligrams of **184** were isolated after purifications by chromatography (either on silica or alumina), and the analyses were inconclusive.

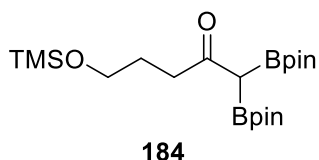
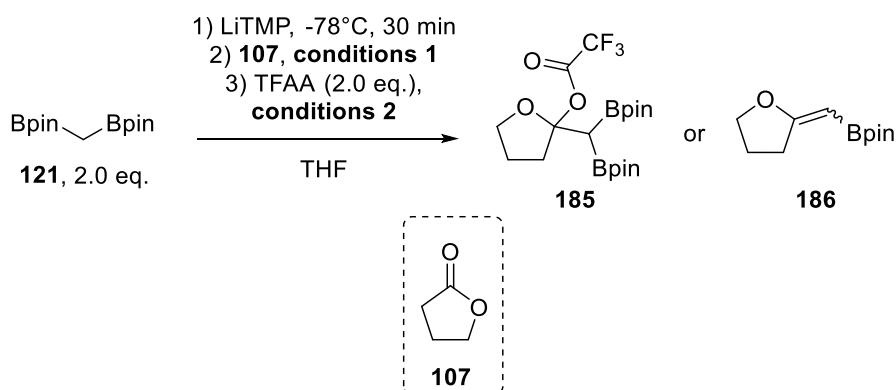


**Figure 21:** Potential silylated side-product **184**.

The trapping of the alkoxide using TFAA was reported by Pelter to initiate an *in situ* olefination process. Accordingly, we replicated his experiment in hope of forming the borylated olefin product **186** (Table 9). However, it has to be noted that Pelter used a  $\text{B}(\text{Mes})_2$  borane as the boryl moiety, more electrophilic than our Bpin boronate. It is therefore probable than the process will go no further than the trapping of the alkoxide, leading to trifluoroacetate **185**.

**Table 9:** Trapping attempts using TFAA.

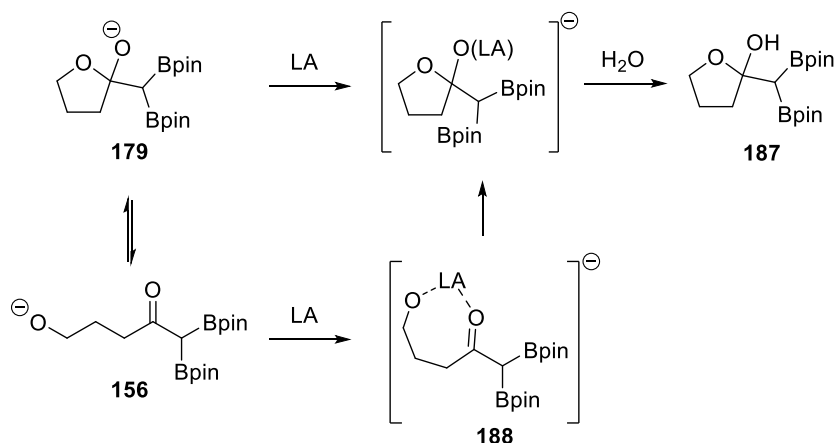


| Entry | Conditions 1 | Conditions 2               | Yield 185 (%) | Yield 186 (%) |
|-------|--------------|----------------------------|---------------|---------------|
| 1     | -78°C, 2h    | -116°C, 1h,<br>then RT, 1h | 0             | 0             |
| 2     | 0°C, 1h      | -78°C, 1h,<br>then RT, 1h  | 0             | 0             |
| 3     | 0°C, 1h      | 0°C, 2h                    | 0             | 0             |

The trapping by trifluoroacetic anhydride, as described by Pelter, is carried out at extremely low temperature. While the addition step was done at -78°C, we used an ethanol/nitrogen cooling bath for the trapping step (**Table 9, Entry 1**). After an hour, the mixture was warmed up to room temperature to facilitate the elimination, but this procedure only resulted in the recovery of both the lactone and the *gem*-bisborylmethane. We raised the temperatures to 0°C for the addition and -78°C for the trapping, with no significant change to the composition of the crude mixture (**Table 9, Entry 2**). Further increasing the temperatures to perform the reaction entirely at 0°C still did not yield trapped product **185**, nor did it produce a significant amount of **186**, though trace signals at 5.36 ppm were detected (**Table 9, Entry 3**).

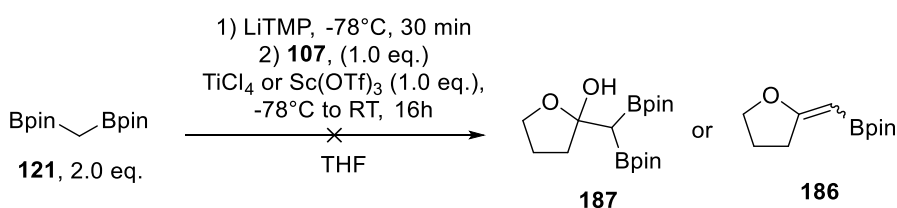
We envisioned that Lewis acids could be alternative trapping agents for our alkoxide intermediate. An aqueous work-up would provoke the hydrolysis of the Lewis acid, liberating the alcohol product **187** (**Scheme**

**76).** This strategy could present another advantage: should the lactone undergo ring-opening, the Lewis acid could act as a template and keep both oxygens at the termini of the chain in close proximity (as illustrated with structure **188**), thus facilitating the reformation of a cyclic intermediate.



**Scheme 76:** Postulated trapping of alkoxide intermediate **179** using a Lewis acid.

In our attempt to trap the alkoxide intermediate in such a way, we selected the strongly electron deficient titanium(IV) chloride, along with the milder scandium(III) triflate (**Scheme 77**). Both reactions failed, leading to similar crude mixtures constituted of the starting borylated reagent and small amount of the lactone.



**Scheme 77:** Trapping attempt using  $\text{TiCl}_4$  and  $\text{Sc}(\text{OTf})_3$ .

None of our attempts to trap the alkoxide intermediate **179** were successful. This study might indicate the inefficiency of the nucleophilic attack of the carbanion (deprotonated **121**) on the lactone under our



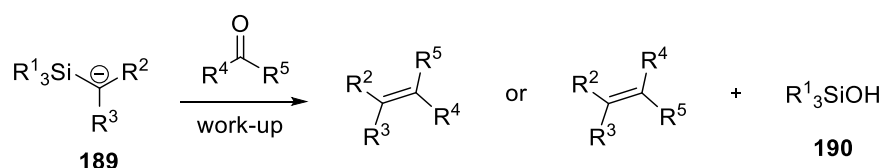
reaction conditions. However, it is also possible that the trapping strategies themselves were not suited to this system.

In light of these latest results, we concluded our work on the boron-Wittig and turned our attention to the silicon-based Peterson olefination.



## 5. The Peterson reaction

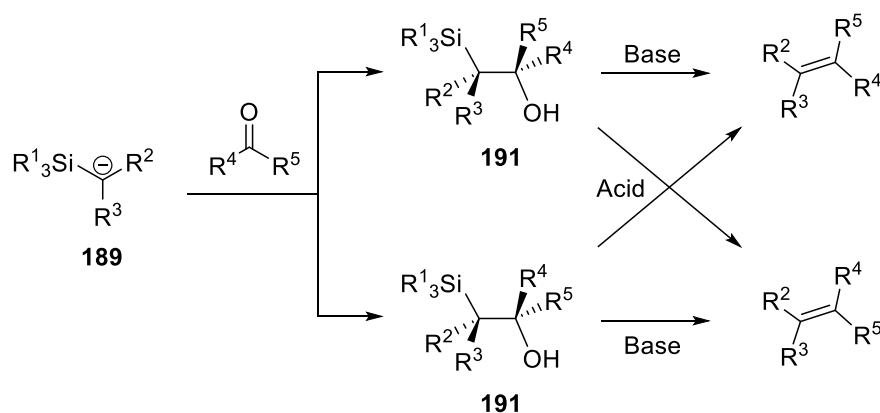
The Peterson olefination has enjoyed sustained interest from the synthetic community since its discovery in the late 1960's.<sup>[161]</sup> This reaction is usually defined as the formation of an alkene from an  $\alpha$ -silyl carbanion **189** and a carbonyl compound (**Scheme 78**). The silylated group is sacrificed in the process, driven to completion by the formation of a volatile siloxane by-product **190**.



**Scheme 78:** General scheme of the Peterson olefination.

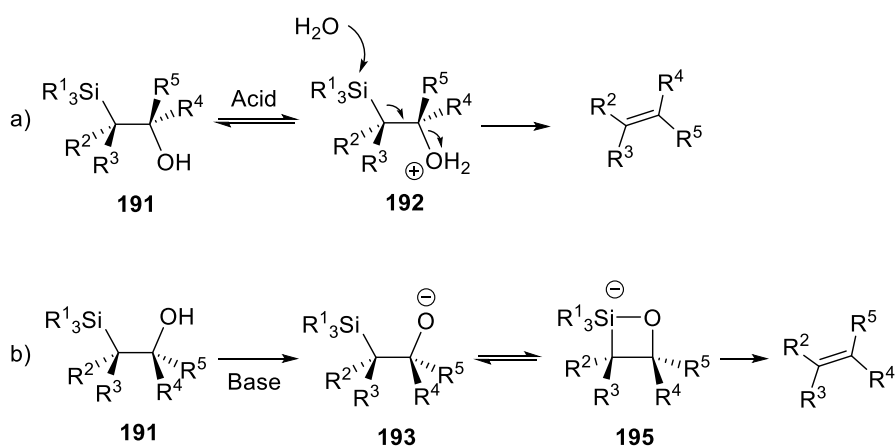
Just as the boron-Wittig reaction is considered as the boron-based counterpart to the traditional Wittig reaction, the Peterson olefination is often referred to as the "silyl-Wittig reaction". One advantage of the Peterson olefination is that the siloxane by-product **190** is usually volatile and thus readily removed in comparison to the non-volatile triphenylphosphine oxide by-product of the Wittig reaction.

More importantly, the second key characteristic of the Peterson is that it can afford both *E* and *Z* isomers depending on the reaction conditions employed (**Scheme 79**). The addition of the carbanion **189** on a carbonyl compound results in the formation of two diastereomeric  $\beta$ -hydroxyalkylsilanes **191**. Interestingly, each of the diastereomers can lead to either of the alkenes.



**Scheme 79:** Stereoselectivity of the Peterson olefination.

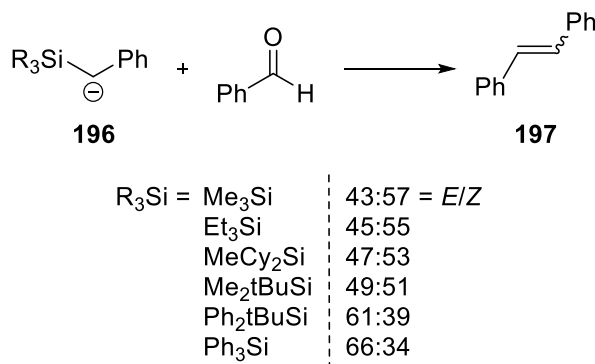
The elimination under acidic conditions proceeds via an oxonium intermediate **192** (Scheme 80, a) from which a E<sub>2</sub>-type process can ensue. The compulsory antiperiplanar conformation governs the stereochemistry of the alkene product. On the other hand, under basic conditions, the elimination proceeds via a mechanism that resembles the one of the Wittig and boron-Wittig reactions, *i.e.* via a four-membered ring **195** (Scheme 80, b). Since the elimination under acidic or basic conditions is stereospecific, the global stereoselectivity of the reaction rely on the addition step (see below **Figure 22**).<sup>[162]</sup>



**Scheme 80:** Proposed mechanism of the Peterson elimination under acidic (a) or basic (b) conditions.

It is worthy of note that the  $\beta$ -hydroxyalkylsilanes intermediate **191**, although frequently isolated in standard Peterson olefination reactions, undergoes spontaneous elimination when the  $\alpha$ -silyl carbanion **189** is substituted with an electron-withdrawing group. This can be rationalized considering that such a group would stabilize the negative charge developed during the elimination. In these situations, the alkene is obtained in the diastereomeric form expected to be favored under basic conditions.

In an in-depth study of the Peterson reaction between  $\alpha$ -silyl benzyl anions **196** and benzaldehyde by Bassindale *et al.*, the ratio of the *E*- and *Z*-stilbene product **197** proved to be insensitive to the nature of the counterion, the solvent, the added salts, the variation of the carbanion-forming base, or the temperature.<sup>[163]</sup> However, they demonstrated the influence of the size of the silyl group, with an observed inversion of selectivity between the small trimethylsilyl group and the bulkier triphenylsilyl (**Scheme 81**).



**Scheme 81:** *cis/trans* selectivity of the Peterson olefination correlated to the silyl group's size.

To explain this selectivity, Bassindale and co-workers proposed a model based on the controlled approach of reagents at a Bürgi-Dunitz angle of *ca* 109° (**Figure 22**). Assuming the non-reversibility of the addition step, the two conceivable orientations of the carbanion during the approach result in the formation of two  $\beta$ -hydroxyalkylsilanes diastereomers **191**. In their model, the phenyl and silyl substituents borne by the carbanion **196**

are represented by a L for the larger and a M for the medium-sized, while the hydrogen is positioned opposite to the carbonyl's oxygen.

The favorable approach reduces the steric hinderance by placing the medium-size group (instead of the larger one) next to the phenyl of the benzaldehyde (**Figure 22**, left). The diastereoselectivity is correlated to the barriers leading to either of the transition states, placing the reaction under kinetic control. When the carbanion is carrying a trimethylsilyl group, the phenyl group is the bulkiest and the *threo* diastereomer is obtained, leading *in fine* to the preferred formation of the *trans* olefin. But as the silyl group's size increases, the priority order of the substituents shifts, altering the diastereomeric ratio.

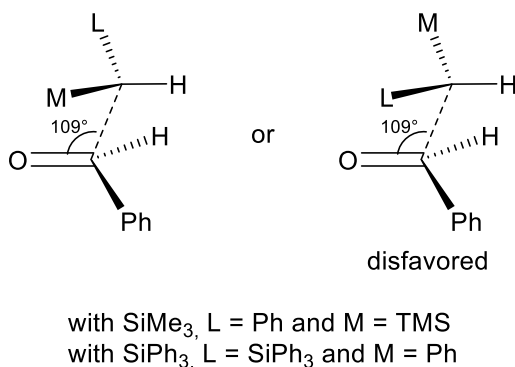


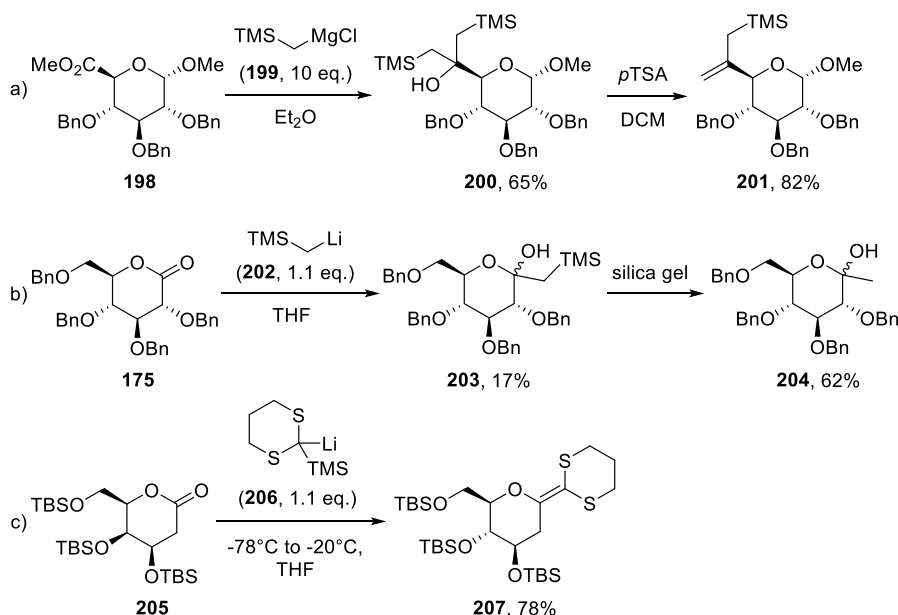
**Figure 22:** Bassindale's model for the selectivity of the Peterson reaction based on steric effects.

Over the years, the Peterson olefination has found broad utility across various carbonyl substrates, including applications with sugar and sugar lactone derivatives. Raadt and Stütz reported the reaction between uronic acid **198** and a large excess of the Grignard **199** (**Scheme 82**, a).<sup>[164]</sup> The compound **200**, resulting from the double addition of the Grignard on the carbonyl group, then proceeded with the siloxane elimination under acidic conditions. The procedure afforded the terminal alkene **201** with a 53% overall yield over two steps. The reaction was carried out on an ester function borne by a sugar substrate, but not on the anomeric carbon.

In a related effort, Glänzer and Csuk described the addition of silylated organolithium reagent **202** to the benzyl protected sugar lactone

**175 (Scheme 82, b).**<sup>[165]</sup> The  $\beta$ -hydroxyalkylsilanes **203** is obtained in a low 17% yield after silica gel chromatography, alongside the desilylated product **204** in 50% yield. To confirm that the alcohol **204** is the result of the protodesilylation of **203** during purification, the latter was stirred on silica gel, affording **204** in 62% yield. However, no subsequent attempts to convert **203** to an alkene via elimination were reported.

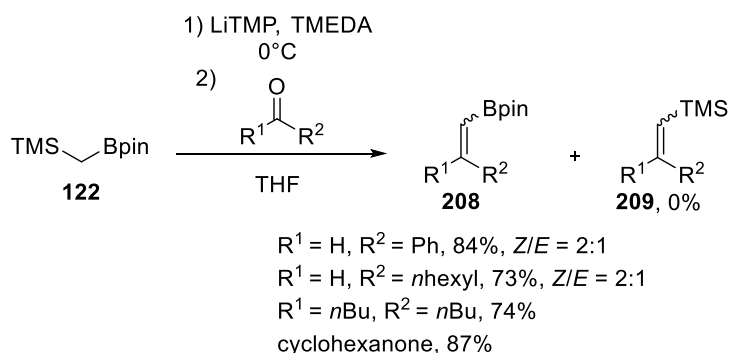
The only recorded successful Peterson reaction on a sugar lactone was achieved by Mlynarski and Banaszek.<sup>[166]</sup> In their study, the 2-deoxy lactone **205**, protected by TBS ethers, reacted smoothly with deprotonated reagent **206** to afford the desired ketene dithioacetal **207** as the sole product in high yield (Scheme 82, c).



**Scheme 82:** Peterson olefination on sugar and sugar lactone substrates.

The synthesis of vinylboronates *via* a Peterson olefination was pioneered by Matteson *et al.*<sup>[167]</sup> Four carbonyl derivatives were reported to react with *gem*-silylboryl methane **122** to form exclusively alkene-boronic esters **208** (Scheme 83). Despite anticipated issues with chemoselectivity, no formation of vinylsilane **209**, indicative of a boron moiety loss as in a boron-Wittig reaction, was observed. A further unexpected result was the

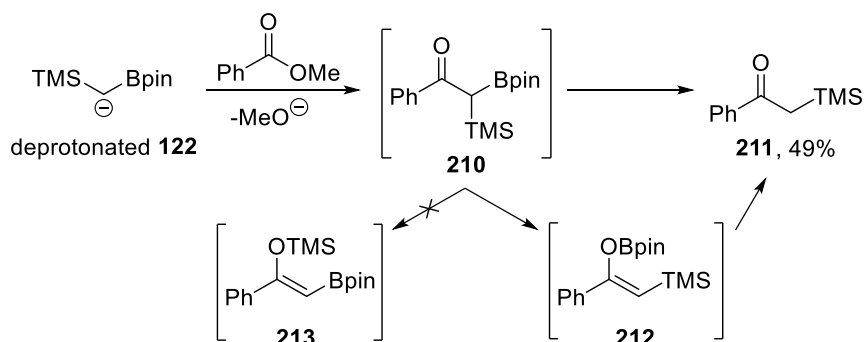
predominance of the *cis* isomer in the alkene boronic esters derived from aldehydes.



**Scheme 83:** Peterson olefination applied to the synthesis of alkenylboronates.

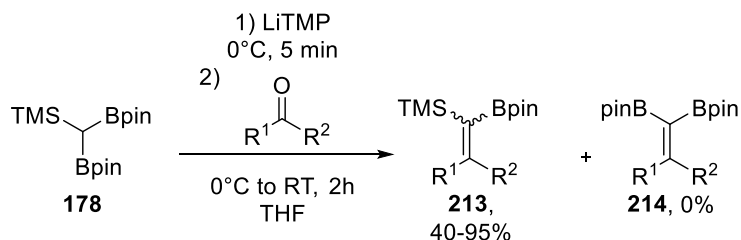
However, when Matteson *et al.* used methyl benzoate ester as the reaction substrate,  $\alpha$ -(trimethylsilyl)acetophenone **211** was obtained as the sole product (**Scheme 84**).<sup>[168]</sup> This transformation proceeded through the initial addition of deprotonated *gem*-silylborylmethane **122** to the ester's carbonyl group, followed by the elimination of the alkoxide moiety, leading to compound **210**. As described for the boron-Wittig (see **Scheme 60**, page 84), a ketone-enol isomerization can occur on this intermediate. While the 1,3-shift of boron from the  $\alpha$ -carbon to the carbonyl oxygen was demonstrated to be rapid in the previous chapter,  $\alpha$ -silyl ketones isomerize readily to silyl enols only upon heating above 100°C.<sup>[169]</sup> Under the reaction conditions, only enol **212** would form, which, upon hydrolysis, led to the observed product **211**.





**Scheme 84:** Matteson's attempt at synthesizing a vinylboronate from an ester.

To the best of our knowledge, the synthesis of vinylboronates *via* a Peterson olefination remained unexploited until the work of Fernández *et al.*, in 2016.<sup>[170]</sup> They reported the deprotonation of *gem*-bisborylsilylmethane **178**, followed by the nucleophilic attack of the carbanion thus formed on a series of cyclic or acyclic ketones (**Scheme 85**). Interestingly, they also observed a total chemoselectivity, although for the boron-Wittig reaction. Nineteen *gem*-silylborylalkenes **213** were obtained in yields ranging from average to excellent, while no bisborylalkene **214**, resulting from a Peterson olefination was observed.



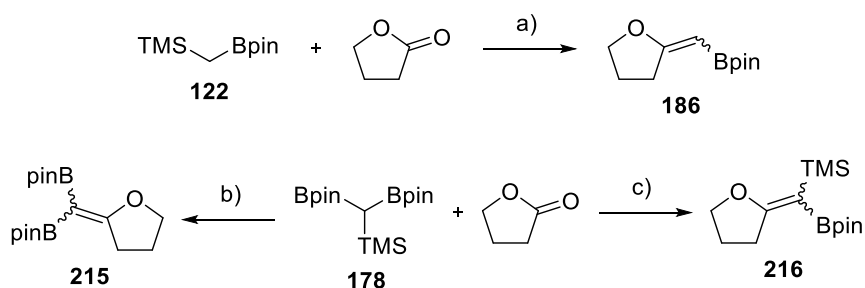
**Scheme 85:** Fernández's olefination of ketones using *gem*-bisborylsilylmethane **178**.

## 5.1. The Peterson olefination for the borylation of lactones

### 5.1.1. Synthesis of the borylated reagents

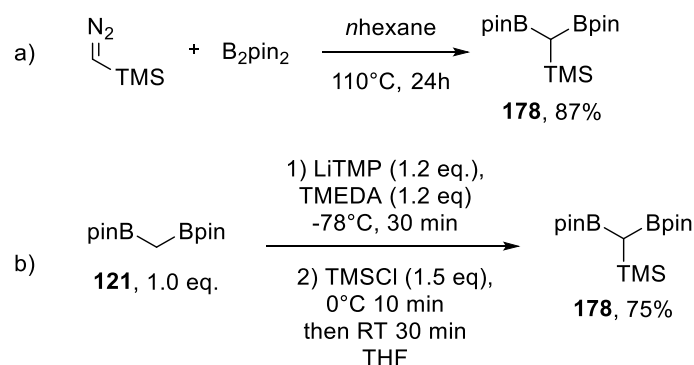
Although not as extensively studied as the boron-Wittig reaction, the Peterson olefination has shown great potential for the synthesis of

vinylboronates. To exploit this olefination for the formation of borylated *exo*-glycols, we planned to study the reaction with simple lactones first. This would require the synthesis of the *gem*-silylborylmethane **122** as well as the *gem*-bisborylsilylmethane **178**. The Peterson olefination of lactones with **122** would lead to alkenylboronate **186** (Scheme 86, a), while the same reaction using **178** would afford an alkenylbisboronate **215** (Scheme 86, b). However, if the chemoselectivity observed by Fernández for the boron-Wittig olefination persists under our conditions, the resulting *gem*-silylboryl olefin **216** would still be a significant advancement in our project (Scheme 86, c).



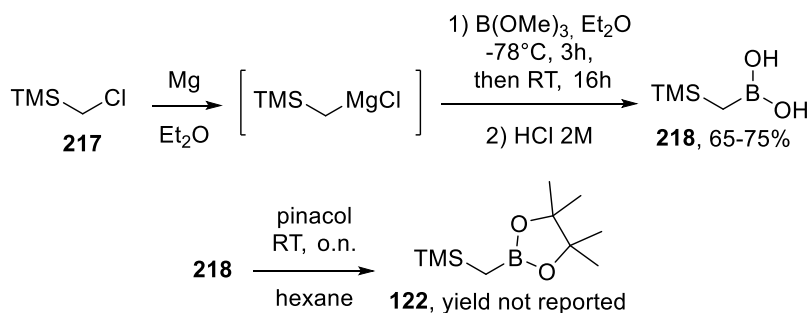
**Scheme 86:** The general scheme of the Peterson olefination of lactone.

Fernández *et al.* obtained their reagent **178** through the insertion of a diazo compound into a boron-boron single bond (Scheme 87, a).<sup>[170]</sup> Rather than attempting to replicate their protocol, we chose to derive **178** from the previously obtained *gem*-bisborylmethane **121**. According to the reaction conditions we developed in Table 7 (see page 96), the deprotonation of **121**, followed by addition to TMSCl, led to **178** in 75% yield (Scheme 87, b).



**Scheme 87:** (a) Fernández's diazo-based synthesis of **178** and (b) our substitution-based alternative.

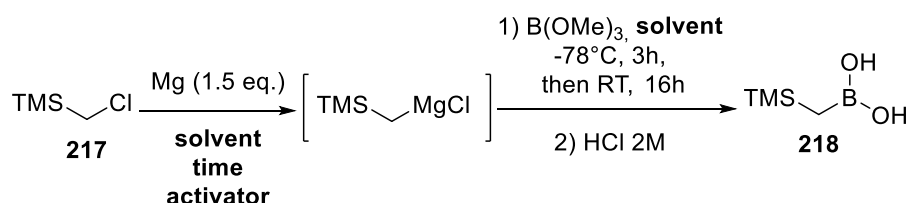
The synthesis of *gem*-silylborylmethane **122** by Matteson relied on the metalation of the corresponding  $\alpha$ -borylchloride **217** (Scheme 88).<sup>[167]</sup> The Grignard thus obtained was then added to trimethyl borate. An aqueous work-up afforded the boronic acid **218**, which was subsequently esterified with pinacol to give the desired product **122**.



**Scheme 88:** Matteson's Grignard-based synthesis of **122**.

As we attempted to replicate this synthesis of boronic acid **218**, the Grignard intermediate proved unwilling to form *in situ*. After the reaction, the magnesium was recovered, rinsed, dried, and weighted. In most cases, more than 95% of the magnesium remained unreacted, illustrating the reluctant metalation of **217**. Several strategies were explored to activate the magnesium (Table 10).

**Table 10:** Synthesis of boronic acid **218**.



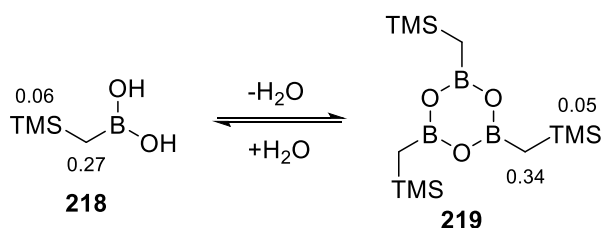
| Entry          | Solvent           | Time | Activator <sup>a</sup>                      | Yield <b>218</b> (%) |
|----------------|-------------------|------|---------------------------------------------|----------------------|
| 1              | Et <sub>2</sub> O | 1h30 | I <sub>2</sub> , heatgun                    | 0                    |
| 2              | THF               | 1h30 | I <sub>2</sub> , heatgun                    | 0                    |
| 3              | Et <sub>2</sub> O | 4h   | I <sub>2</sub> , heatgun                    | 0                    |
| 4              | Et <sub>2</sub> O | 16h  | I <sub>2</sub> , oil bath                   | 0                    |
| 5              | Et <sub>2</sub> O | 1h30 | FeCl <sub>3</sub> , heatgun                 | 0                    |
| 6              | Et <sub>2</sub> O | 1h30 | Ultrasound                                  | 0                    |
| 7              | Et <sub>2</sub> O | 1h30 | (BrCH <sub>2</sub> ) <sub>2</sub> , heatgun | 73 <sup>b</sup>      |
| 8 <sup>c</sup> | Et <sub>2</sub> O | 1h30 | (BrCH <sub>2</sub> ) <sub>2</sub> , heatgun | 57                   |

*a.* Reaction mixture heated to reflux, except for entry 6, which proceeded at RT; *b.* average across 11 reactions; *c.* simultaneous addition of the Grignard and the borate.

When the *in situ* formation of the Grignard reagent failed, as evidenced by the recovery of most of the involved magnesium, the addition step on the borate reagent was not pursued (**Table 10, Entries 1-6**).

The addition of a drop of dibromoethane (BrCH<sub>2</sub>)<sub>2</sub> in the reaction medium proved to be the suitable activation strategy for the magnesium (**Table 10, Entry 7**). This, along with diethyl ether as a solvent, the use of fresh magnesium turnings, and the addition of the chloride **217** by portion, allowed for a successful metalation to occur. The subsequent addition of the Grignard to the borate reagent led to the formation of the desired boronic acid. This optimized procedure was conducted eleven times during this thesis, yielding a cumulative 28 grams of **218**, in yield ranging from 67%

to 83%. Interestingly, two sets of signals that could match the expected product were observed by  $^1\text{H}$  NMR. They correspond to the boronic acid **218**, in equilibrium with its trimer form **219** (**Scheme 89**) in a *ca* ratio 1:2; this proportion varying slightly from one batch to another. The trimerization of boronic acid is a known phenomenon, and both forms are considered to have the same reactivity, hence no efforts were made towards the exclusive formation of the monomer.<sup>[171]</sup>



**Scheme 89:** Trimerization of the boronic acid **218** and the  $^1\text{H}$  NMR shifts in ppm of the corresponding signals.

With this efficient method for the activation of magnesium in hand, we attempted to increase the yield by following Matteson's protocol for the borylation step. Up to this point, we had been adding the Grignard to a diethyl ether solution of the boronate reagent directly (**Table 10, Entries 1-7**), Matteson indicated that both the Grignard and the boronate should be placed in separate addition funnel, and poured concomitantly in a flask containing diethyl ether at  $-78^\circ\text{C}$  (**Table 10, Entry 8**). This modification led to a decreased yield and the emergence of a side-product **220**. While the boronic acid and its trimer can be found at 33.2 ppm and 31.3 ppm on a  $^{11}\text{B}$  NMR spectra, the new compound **220** is characterized by a signal at 54.0 ppm. This is consistent with a borinic acid shift, suggesting that **220** could result from a double addition of the Grignard onto the boron center (**Figure 23**).

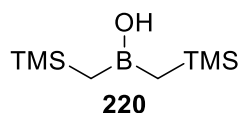
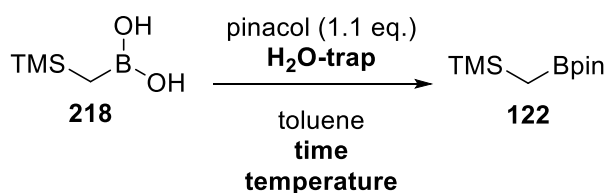


**Figure 23:** Postulated over addition side-product **220**.

The crude obtained in this instance was purified according to Matteson's instruction, *i.e.* by recrystallization in water. Although this did not improve the purity of the crude, we noticed a modification of the boronic acid/trimer ratio from 4:1 to 1:2. Considering that the large excess of water used for the recrystallization would shift the equilibrium towards the boronic acid form, this allowed us to confidently assign the NMR signals of **218** and **219**.

The esterification of the obtained boronic acid (or its trimer) was the next step of the synthesis. The use of a diol such as pinacol to esterify a boronic acid is a standard and straightforward process, usually requiring high temperatures and a setup to capture the released water, such as a Dean-Stark apparatus. Surprisingly, the esterification of boronic acid **218** (used as a monomer/trimer mixture) proved to be challenging (**Table 11**).

**Table 11:** Direct esterification of **218** attempts.



| Entry          | Time | Temperature | H <sub>2</sub> O-trap | 218/122 |
|----------------|------|-------------|-----------------------|---------|
| 1 <sup>a</sup> | 16h  | RT          | /                     | 1 : 1   |
| 2              | 16h  | 110°C       | /                     | 1 : 1.2 |
| 3              | 16h  | 110°C       | Dean-Stark            | 1 : 2   |
| 4              | 72h  | 110°C       | Dean-Stark            | 1 : 1.5 |
| 5              | 16h  | 110°C       | Molecular sieve (4 Å) | 1 : 2   |
| 6              | 16h  | 110°C       | MgSO <sub>4</sub>     | 1 : 2   |
| 7 <sup>b</sup> | 16h  | 110°C       | /                     | 1 : 2.5 |
| 8 <sup>b</sup> | 16h  | 110°C       | Molecular sieve (4 Å) | 1 : 2.5 |

*a. the reaction was carried out in nhexane; b. the reaction was carried out in the presence of 1.1 equivalent of pyridine.*

We began with the conditions reported by Matteson (**Table 11, Entry 1**). The esterification carried out in hexane at room temperature led to an equal mixture of the desired pinacol ester **122** and the unreacted boronic acid **218**. We switched the solvent for toluene so that the reaction can be heated more strongly, resulting in a slight improvement of the acid/ester ratio (**Table 11, Entry 2**).

Water-trapping strategies were put in motion to further facilitate the esterification. The flask was equipped with a Dean-Stark apparatus, and subsequent reaction refluxed overnight in toluene resulted in a better conversion of the starting material **218**, with a two-to-one ratio in favor of the ester **122**. Extending the reaction to three days failed to allow for a better conversion (**Table 11, Entry 4**). The reaction was carried out in the presence of molecular sieve (**Table 11, Entry 5**) or magnesium sulfate (**Table 11, Entry 6**) in the reaction medium to capture the water, leading to the same crude composition as the one obtained with a Dean-Stark apparatus.

We envisioned that a base could encourage the esterification process. Pyridine was selected for its adequate boiling point, above the one of water and toluene. The reaction resulted in a further improvement of the boronic acid conversion, even in the absence of a desiccant agent (**Table 11, Entry 7**). Adding molecular sieves did not notably affect the outcome (**Table 11, Entry 8**).

The challenges in esterifying **218** were unexpected, as the esterification of boronic acids is generally straightforward and widely documented. To explain the difficult esterification of our substrate, we considered the impact of a silicon atom geminal to the boron (**Figure 24**). The donating C-Si  $\sigma$  orbital may partially overlap with the empty p orbital of the boron. This positive hyperconjugation effect, aligned with the  $\beta$ -silicon effect stabilizing adjacent carbocations, would reduce the electrophilicity of the boron, thereby hindering the attack of a nucleophile such as the pinacol.

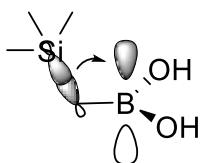
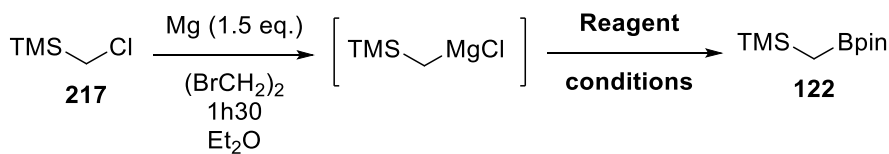


**Figure 24:** Hyperconjugation of the C-Si  $\sigma$  orbital stabilizing adjacent the boron group.

Although a purification of the acid/ester mixture can be considered, our interest was instead turned to the possibility of forming the ester directly and not *via* the boronic acid. To achieve this, suitable boron sources were selected and used during the Grignard procedure in place of the trimethyl borate (**Table 12**).

**Table 12:** Synthesis of boronic ester **122**.



| Entry | Reagent                         | Conditions | <b>218/122</b>             |
|-------|---------------------------------|------------|----------------------------|
| 1     | HBpin                           | RT, 1h     | 1 : 5                      |
| 2     | B <sub>2</sub> pin <sub>2</sub> | RT, 1h     | 6 : 1                      |
| 3     | <i>i</i> PrOBpin                | RT, 1h     | 1 : 9                      |
| 4     | <i>i</i> PrOBpin                | RT, 2h     | 0 : 100 (74%) <sup>a</sup> |

*a. In brackets, yield in pure product after purification by distillation.*

The first boron reagent we tested was the pinacol borane HBpin (**Table 12, Entry 1**). Satisfyingly, the desired boronic ester was obtained as the major constituent of the crude mixture. The presence of boronic acid **218**, however, was not expected. Nonetheless, the ratio between these two compounds was more interesting than in our previous esterification attempts. The borylation step was also more convenient, a quick one-hour process at room temperature instead of the lengthy protocol described by



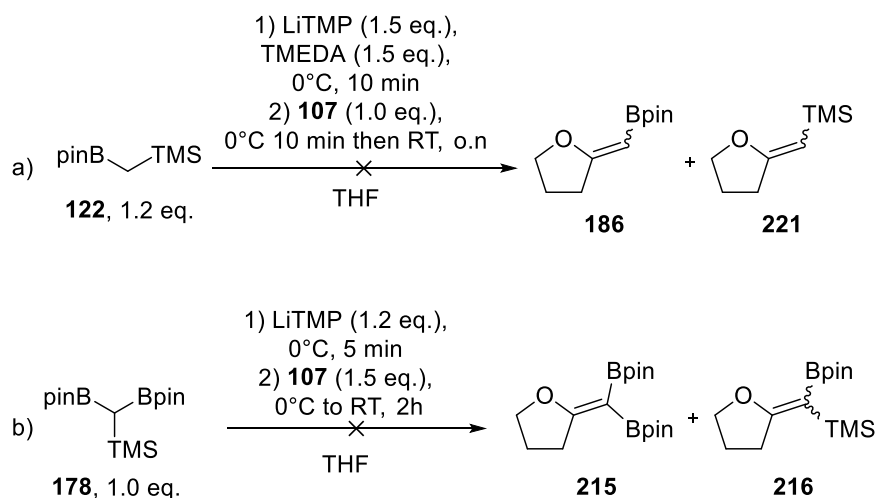
Matteson. Bispinacolatodiboron  $B_2pin_2$  was also tested, but the crude mixture obtained was mainly composed of the boronic acid (**Table 12, Entry 2**).

On the other hand, the use of isopropoxypinacolboronate *iPrOBpin* resulted in an improved selectivity toward the ester formation (**Table 12, Entry 3**). Doubling the borylation time completely suppressed the boronic acid formation (**Table 12, Entry 4**). This, however, didn't mean that the crude was exempt of impurities. A purification via flash chromatography was performed and the pure **122** was obtained in the somewhat low yield of 47%. The reaction was repeated and the crude was instead distilled under reduced pressure affording the pure product in 72% yield. Two additional batches were made during this thesis, with yields of 58% and 91%. Although the purification efficiency appears to be inconsistent, 14.6 grams of product were produced this way.

The presence of the boronic acid **218** in some of our crude mixture is difficult to justify (**Table 12, Entries 1-3**). Although the reaction is quenched with an aqueous saturated solution of  $NH_4Cl$  to destroy the unreacted Grignard, these conditions are not sufficient to hydrolyze the desired ester **122** (as seen in **Table 12, Entry 4**). Therefore, it was hypothesized that the boronic acid originated from the hydrolysis of an unknown side-product.

#### 5.1.2. Peterson olefination attempts on lactone

With both *gem*-bisborylsilylmethane **178** and *gem*-silylborylmethane **122** at our disposal, we naturally started our study of the Peterson olefination by replicating Matteson's and Fernandez's conditions, albeit using lactone **107** as the substrate (**Scheme 90**).



**Scheme 90:** Peterson olefination attempts on lactone.

Matteson's protocol, applied to lactone, gave a crude mixture mainly composed of the starting *gem*-silylborylmethane **122** (Scheme 90, a). Neither the borylated derivative **186** nor the silylated one **221** were observed. The reaction using *gem*-bisborylsilylmethane **178** led to the partial recovery of the borylated reagent, with no traces of either the bisborylenol ether **215** or the silylborylenol ether **216** detected (Scheme 90, b).

In the absence of encouraging results, and before any attempt at optimizing the reaction conditions, we decided to learn more about the Peterson olefination of  $\alpha$ -borylated reagents using aldehydes and ketones.

## 5.2. Investigation of the Peterson olefination using aldehydes and ketones

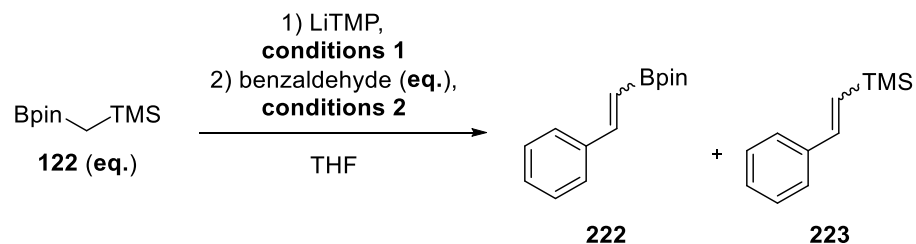
While the synthesis of vinylboronate *via* a Peterson olefination has been reported, no systematic study of this transformation has been performed. We decided to complement this work by conducting an experimental and computational study of the Peterson olefination using *gem*-borylsilylalkane reagents. The objectives are triple:

- to assess the influence of the nature of the carbonyl compound, the borylated group, and the silylated group, that have been overlooked so far;
- to rationalize the stereoselectivity and the Peterson vs boron-Wittig chemoselectivity;
- to identify the optimal boryl and silyl group couple for the synthesis of vinylboronates.

#### 5.2.1. Optimization of the conditions for the Peterson olefination

In order to conduct the experimental side of this study, we first needed to optimize the reaction conditions. To this end, we explored the reaction of benzaldehyde, as a reference substrate, with **122**, each equivalent of this borylated reagent being deprotonated by 1.2 equivalents of LiTMP as a base (**Table 13**).

**Table 13:** Optimization of the Peterson olefination between benzaldehyde and **122**.



| Entry | Eq. of <b>122</b> | Eq. of benzald. | Conditions 1                | Conditions 2              | Yield <sup>a</sup> <b>222</b> (%) | Z/E   | Yield <sup>a</sup> <b>223</b> (%) |
|-------|-------------------|-----------------|-----------------------------|---------------------------|-----------------------------------|-------|-----------------------------------|
| 1     | 1.3               | 1.0             | TMEDA 1.4 eq<br>0°C, 2h30   | -78°C, 2h30, then RT, 16h | 0                                 |       | 0                                 |
| 2     | 1.3               | 1.0             | 0°C, 15 min                 | -78°C, 1h, then 0°C, 2h   | 0                                 |       | 0                                 |
| 3     | 2.0               | 1.0             | TMEDA 2.0 eq<br>0°C, 10 min | 0°C to RT, 16h            | 0                                 |       | 0                                 |
| 4     | 1.0               | 1.5             | 0°C, 5 min                  | -78°C to RT, 2h           | traces                            |       | 0                                 |
| 5     | 1.0               | 1.0             | 0°C, 5 min                  | 0°C to RT, 2h             | 47                                | 2 : 1 | 0                                 |

| Entry           | Eq. of 122 | Eq. of benzald. | Conditions 1                  | Conditions 2           | Yield <sup>a</sup> 222 (%) | Z/E     | Yield <sup>a</sup> 223 (%) |
|-----------------|------------|-----------------|-------------------------------|------------------------|----------------------------|---------|----------------------------|
| 6               | 1.5        | 1.0             | 0°C, 5 min                    | 0°C to RT, 2h          | 49                         | 2 : 1   | 0                          |
| 7               | 2.0        | 1.0             | 0°C, 5 min                    | 0°C to RT, 2h          | 56                         | 2 : 1   | 0                          |
| 8               | 3.0        | 1.0             | 0°C, 5 min                    | 0°C to RT, 2h          | 19                         | 3 : 1   | 0                          |
| 9               | 2.0        | 1.0             | TMEDA 2.2 eq,<br>0°C, 5 min   | 0°C to RT, 2h          | 55                         | 2 : 1   | 0                          |
| 10 <sup>b</sup> | 2.0        | 1.0             | 0°C, 5 min                    | 0°C to RT, 2h          | 35                         | 2.5 : 1 | 0                          |
| 11              | 2.0        | 1.0             | 0°C, 5 min, Et <sub>2</sub> O | 0°C to RT, 2h          | 0                          |         | 0                          |
| 12              | 2.0        | 1.0             | 0°C, 5 min, anisole           | 0°C to RT, 2h          | 0                          |         | 0                          |
| 13              | 2.0        | 1.0             | 0°C, 5 min, toluene           | 0°C to RT, 2h          | 0                          |         | 0                          |
| 14              | 2.0        | 1.0             | 0°C, 5 min                    | 0°C then reflux 2h     | 20                         | 3 : 1   | 0                          |
| 15              | 2.0        | 1.0             | 0°C, 5 min                    | -78°C, 1h, then RT, 2h | 37                         | 3 : 1   | 0                          |

*a. NMR yield determined on the crude mixture by using DMT as an internal standard. b. Reaction carried out in dispenser THF.*

Matteson's conditions were the first to be tested (**Table 13, Entry 1**).<sup>[167]</sup> No borylated **222** or silylated styrene **223** are observed by <sup>1</sup>H NMR analysis. The reagent **122** is partially recuperated, and a small amount of benzaldehyde, although volatile, can be observed. Furthermore, additional aromatic peaks are presents, and a singlet around 4.70 ppm is observed. Those signals combined suggest the formation of benzyl alcohol as a side-product of the reaction. The formation of benzyl alcohol from benzaldehyde would typically be carried out through a borohydride-mediated reduction. While a boron atom is indeed present in the reaction mixture, the origin of the hydride is unknown.

Next, we tried Pattison's conditions (**Table 13, Entry 2**),<sup>[172]</sup> as well as those we optimized for the substitution of *gem*-bisborylmethane **121** (see **Table 7**, page 96) (**Table 13, Entry 3**). In both cases, a crude mixture similar to the one obtained in **Entry 1** was obtained.

Fernández's conditions were the first to yield traces of the borylated product (**Table 13, Entry 4**).<sup>[170]</sup> The crude was mainly composed of starting materials, and the benzyl alcohol side-product. A quantitative <sup>1</sup>H NMR was performed, but the signals corresponding to **222** was too low for the yield to be trustworthy. As indications, the *Z/E* ratio was 5:1, and the **222/122** ratio was around 1:17.

When the reagents are used in equimolar proportion (instead of the aldehyde excess advised by Fernández) and the addition step is done at higher temperatures, the quantity of formed product increased drastically (**Table 13, Entry 5**). Starting materials and benzyl alcohol were however detected in the crude by <sup>1</sup>H NMR. The observed *Z/E* ratio was 2:1. A 1.5 equivalents excess of **122** did not modify significantly the outcome of the reaction (**Table 13, Entry 6**), however the yield jumped to 56% when a 2.0 equivalents excess was used (**Table 13, Entry 7**). Augmenting further the amount of borylated reagent revealed to be damaging for the formation of the desired product **222** (**Table 13, Entry 8**). Moreover, the addition of the TMEDA lithium-trap showed no significant influence on the reaction's result (**Table 13, Entry 9**).

The reaction was carried out in THF coming from the anhydrous solvent dispenser mentioned earlier in this thesis (**Table 13, Entry 10**). The

lower yield confirms our previous comment on olefination processes using this machine's solvent (see discussion page 79-83). Other ethereal solvents were tested, but the diethyl ether (**Table 13, Entry 11**) and the anisole (**Table 13, Entry 12**) led only to the recovery of unreacted **122** and benzaldehyde. The reaction carried out in toluene didn't allow for the formation of **222**, and only benzyl alcohol can be found alongside the reagents (**Table 13, Entry 13**).

A higher reaction temperature was tested in order to further encourage the elimination process (**Table 13, Entry 14**). A reflux maintained during two hours after the addition at 0°C worsened the desired product yield and generally degraded the reaction mixture. We performed the reaction at lower temperatures for the beginning of the addition step hoping to see modifications of the stereo- and/or chemo-selectivity. The borylated product was obtained, albeit in a mediocre yield, and in a 3:1 *Z/E* ratio, a very little variation from the usual 2:1 mixture (**Table 13, Entry 15**).

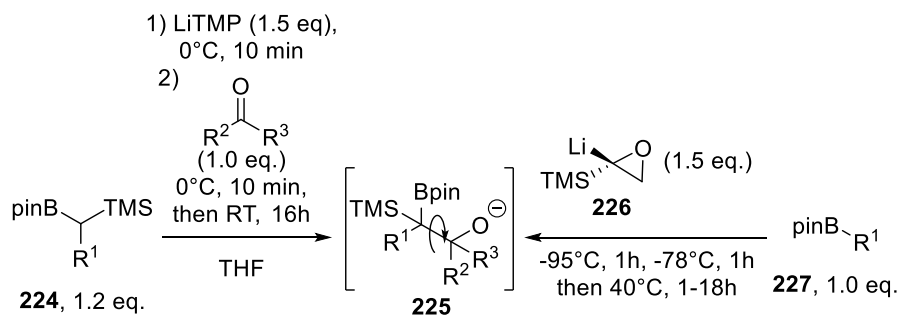
As shown in **Table 13**, none of our conditions led to the formation of silylated product **223**, not even in traces. This total chemoselectivity for the Peterson elimination aligns with the conclusion of Matteson's work on the same *gem*-silylborylmethane **122**.<sup>[167-168]</sup>

The best conditions for the conversion of benzaldehyde, ended up being the reaction in THF of two equivalents of **122**, deprotonated and added onto the benzaldehyde at 0°C, followed by a warm up to RT over two hours to favor the elimination process.

#### 5.2.2. Influence of substituents

The reaction between a carbonyl compound and a *gem*-borylsilylalkane **224** leads to intermediate **225** (**Scheme 91**, left). From this alkoxide, a cyclization toward a four membered ring can occur involving either the boron or the silicon, enabling the subsequent elimination with the oxygen. Although this chemoselectivity has not been studied in the context of a borylating Peterson olefination, the Si-O/B-O elimination competition from **225** was explored by Aggarwal *et al.*<sup>[173]</sup> During their work on boronic esters homologation, they formed intermediate **225** (with R<sup>2</sup> =

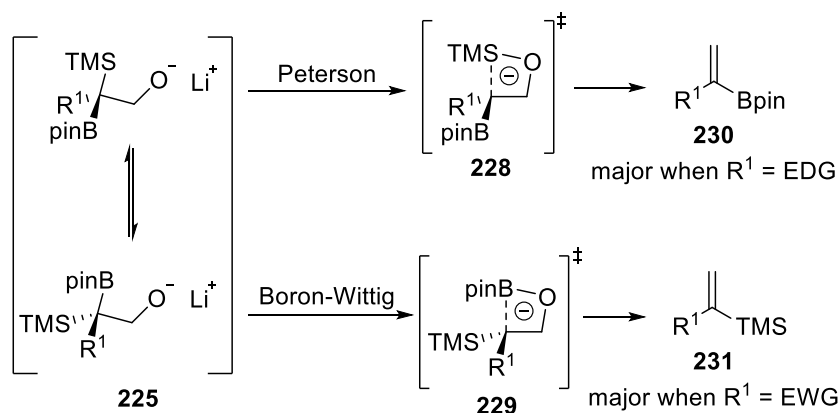
R<sup>3</sup> = H) by adding an epoxide carbanion **226** on borylated reagent **227** (**Scheme 91**, right).



**Scheme 91:** Alkoxide intermediate obtained *via* Peterson olefination (left) or Aggarwal's work (right).

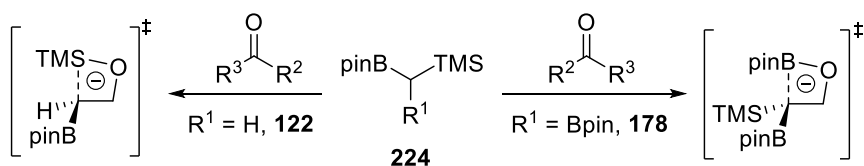
From the intermediate **225**, a four-membered ring forms by bonding the oxygen with either the silicon or the boron group, leading to **228** and **229** respectively (**Scheme 92**). Variations in the Peterson/boron-Wittig chemoselectivity were noticed experimentally and confronted with theoretical results, obtained through a computational study. To rationalize these observations, Aggarwal *et al.* put forward the electronic properties of the R<sup>1</sup> substituents. In the transition state, a negative charge develops on the carbon bearing the boryl/silyl group. If the R<sup>1</sup> substituent can stabilize this charge, the boron group is available to perform a boron-Wittig elimination. Otherwise, the boron group will be needed for the stabilization, rendering it unavailable for the formation of the four-membered ring, and the silicon-based Peterson elimination will occur instead.





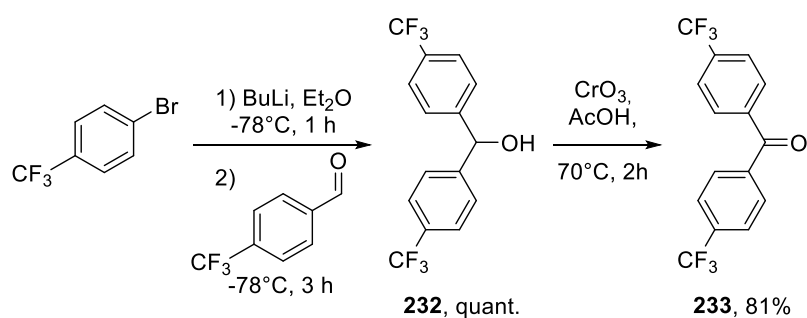
**Scheme 92:** chemoselectivity study by Aggarwal *et al.*

Aggarwal study could be used to justify the opposite chemoselectivities reported by Matteson and Fernández. The *gem*-silylborylmethane **122** of Matteson has no substituent, therefore the boron group is exploited to stabilize the negative charge and the reaction proceeds with the Peterson elimination (**Scheme 93**, left). In Fernández's work, one of the boron groups of the *gem*-bisborylsilylmethane **178** is also used to stabilize the charge, but a second borylated group is free to form the ring with the oxygen and proceeds with the boron-Wittig elimination (**Scheme 93**, right).



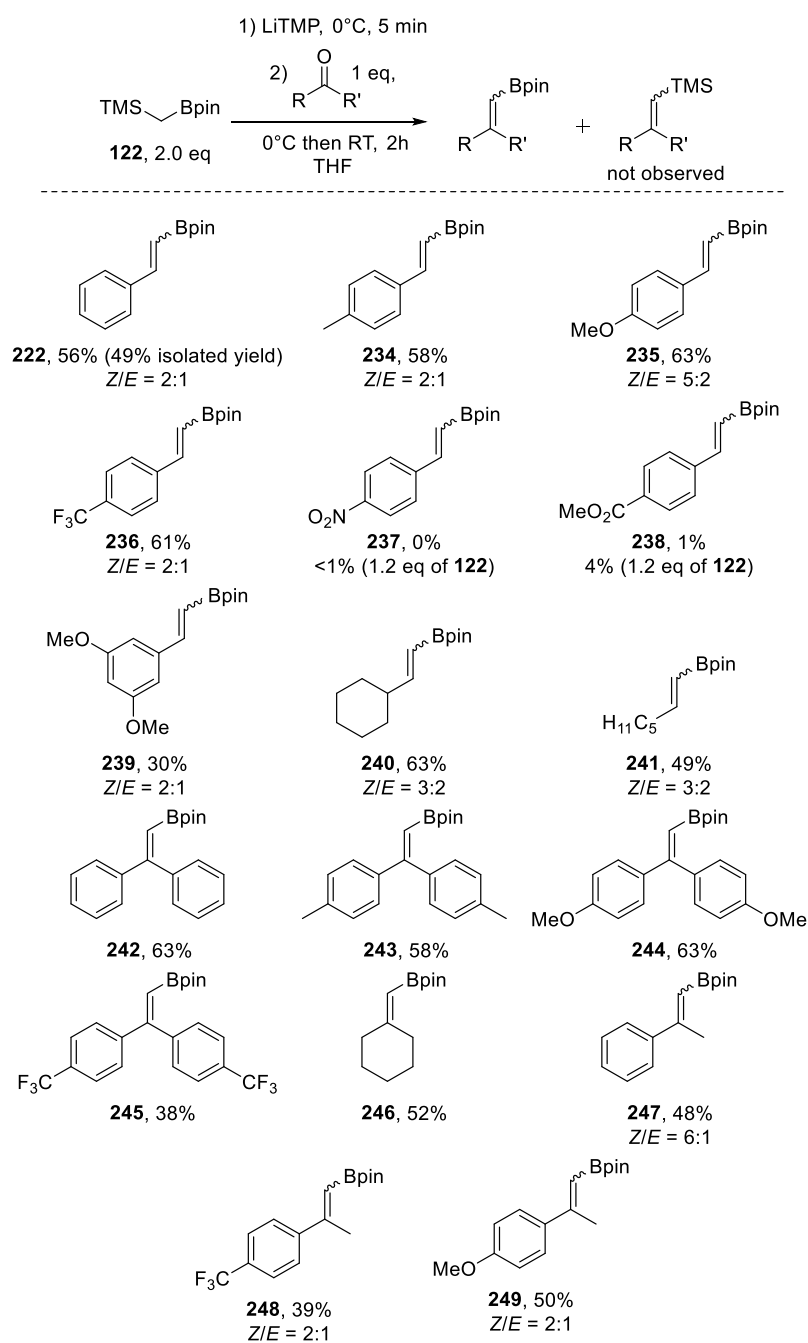
**Scheme 93:** Matteson and Fernández's opposite chemoselectivities.

To study the influence of the nature of the carbonyl substrate on the chemoselectivity, a collection of aldehydes and ketones were transformed into the corresponding boryl/silyl alkenes. This library of substrates was designed to cover a range of electronic properties. All the carbonyl compounds were commercially available, except for the bis(*p*-(trifluoromethyl)phenyl)ketone **233** which was obtained in two steps *via* alcohol **232** (**Scheme 94**).<sup>[174]</sup>



**Scheme 94:** Two-steps synthesis of ketone **233**.

The carbonyl substrates were put in reaction under the optimized reaction conditions described in **Table 13, Entry 7**. In every case, no silylated product was observed, demonstrating that the total chemoselectivity for the Peterson olefination is independent of the electronic properties of the carbonylated reagent. Yields for the formation of the borylated products and the *Z/E* isomer ratio, both measured by  $^1\text{H}$  NMR, are reported in **Scheme 95**.



*Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard.*

**Scheme 95:** Scope of the Peterson olefination using **122**.

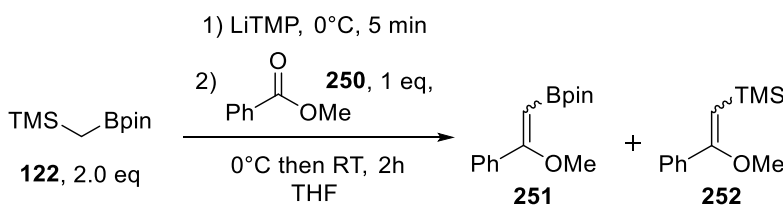
Compare to the reference compound **222**, the electron enriched **234** and **235** products were obtained in similar yields and isomer ratio. However, when electron withdrawing groups were present on the substrates, surprising results were obtained. While the CF<sub>3</sub> *para*-substituted benzaldehyde reacted to give **236** in expected yield, the corresponding dimethoxy-substituted aldehyde led to **239** in lower yields, and the syntheses of borylated alkenes **237** and **238** proved ineffective, supposedly due to side-reactions between the organolithium species and the nitro/ester substituents. Lowering the excess of organolithium allowed for the formation of the desired borylated products, but only in traces quantities.

These results were puzzling as we assumed electron poor carbonyl groups would display an enhanced electrophilicity, rendering the attack of the organolithium specie more favorable. In contrast, electron donating substituents diminish the electrophilicity of the carbonyl, which did not translate into lower yields. These observations suggest that the addition step is not the rate determining step in the olefination sequence. Nevertheless, carbonyl substituents have an influence on reactivity as electron-withdrawing substituents disfavor the reaction. The Peterson/boron-Wittig selectivity, on the other hand, is impervious to the substitution of the carbonyl, with the exclusive Peterson olefination pathway being observed in all cases.

Ketones were also converted successfully, providing tri-substituted alkene boronates in similar yields as for aldehydes. Notably, **247** was obtained in a higher proportion of the *Z* form. This observation contradicts Bassindale's model (see **Figure 22**, page 108), in which the introduction of the methyl group would narrow the difference in bulkiness between the two groups borne by the carbonyl function. Consequently, the preference between the two possibilities for the addition step should be less pronounced, and the isomer ratio should therefore be more balanced. In fact, the higher *Z/E* selectivity observed for **247** can be attributed to the volatility of the *E* isomer, as evidenced by the progressive increase in the *Z/E* ratio over time under reduced pressure.

Interestingly, enolizable aliphatic substrates such as aldehydes **240-241** and ketones **246-249** could also be employed.

Additionally, the reaction with an ester, methylbenzoate **248**, was attempted (**Scheme 96**). Neither the borylated product **249** nor the silylated product **250** were formed; the crude mixture being mainly composed of the starting materials, **122** and **248**. Nevertheless, traces of a new compound could be observed, as indicated by two doublets in  $^1\text{H}$  NMR. The shift and the multiplicity of these signals<sup>i</sup> could correspond to the *Z* and *E* isomers of a disubstituted alkene. However, such substitution patterns would be difficult to explain from a mechanistic point of view, as both the oxygens from the ester would need to be eliminated.



**Scheme 96:** Olefination of ester **250**.

### 5.2.3. Nature of the boryl group

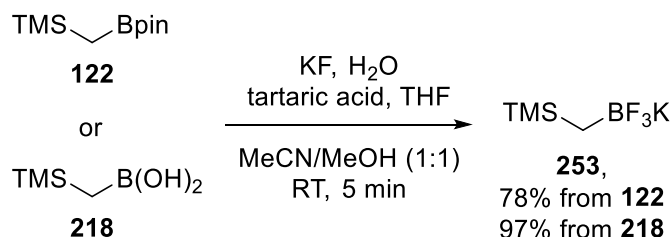
During our work on the boron-Wittig, we envisioned that the perfluorination of the Bpin moiety would increase its electrophilicity, and therefore favor the elimination process leading to the desired olefin (see chapter 4.3.1., page 85). Similarly, the chemoselectivity, whether it follows a Peterson or a boron-Wittig process, could depend on the nature of both the boryl and silyl groups. To investigate this potential influence, we synthesized a series of *gem*-borylsilylmethanes exhibiting different steric and electronic properties.

#### 5.2.3.1. Trifluoroborates

The trifluoroborate derivative **253** was obtained via Lloyd-Jones's protocol, already described in this thesis (see **Scheme 64**, page 88).<sup>[146]</sup> This reaction has been reported starting from either a pinacolboronic esters

<sup>i</sup> at 6.94 ppm (d, *J* = 18.9 Hz) and 5.77 ppm (d, *J* = 14.6 Hz).

such as **122** or boronic acids like **218**.<sup>[175]</sup> Both of the borylated substrates were efficiently converted, with the boronic acid **122** leading to an almost quantitative transformation (**Scheme 97**). The reaction allows for a straightforward purification of **253**, as most of the impurities are simply filtered out or washed out.



**Scheme 97:** trifluoroborate synthesis from **122** or **218**.

As the potassium salt **253** proved insoluble in most organic solvent, and therefore incompatible with the use of organolithium reagent, we endeavor to improve the solubility by using an organic counter-cation. A salt metathesis reaction was exploited to afford tetrabutylammonium salt **254**, albeit in a disappointing 24% yield (**Scheme 98**). In contrast, the cation exchange of various aryl and vinyl trifluoroborates have been reported by Batey and Quach in yields superior or equal to 80%.<sup>[176]</sup> Our substrate **253** proved difficult to solubilize in the quantity of solvent indicated in their protocol. Furthermore, the salt reported in their work either precipitated or “oiled out” of the solution, driving the reaction to completion. No such phenomena were observed in our case, indicating that our product **254** has a higher affinity for the aqueous phase, which could justify our lower yield. The use of a counter anion other than a hydroxide (such as a perchlorate) would provoke the precipitation of the potassium side-product and provide a way around this issue.



**Scheme 98:** Trifluoroborate cationic exchange.

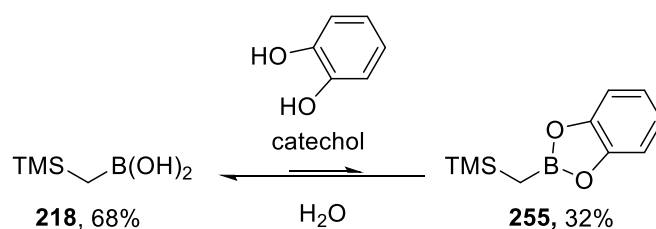
One should note that a very convenient synthetic method was recently reported by Perrin *et al.* and could provide an alternative route towards trifluoroborates.<sup>[177]</sup>

#### 5.2.3.2. Catechol boronate (Bcat)

While many possibilities (such as trifluoroborates) exist to provide a boron group less electrophilic than a Bpin, the opposite cannot be said. By nature, a boron group more electrophilic than a Bpin would also be less stable, and thus more challenging to synthesize. In consequence, very few options of electrophilic boronic esters were reported, and the more common one is the catechol ester.

The exploration of the synthetic method for the Bpin derivatives **122** was used as a probe to identify a viable route towards the catechol ester **255**. The protocols offering promising results were then adapted with the use of catechol-based reagents. The esterification of an isolated boronic acid was disregarded, considering its inefficiency for the formation of pinacol boronic ester. Additionally, the optimized synthesis of **122**, using *i*PrOBpin, was ignored, since its catechol version would require *i*PrOBcat, commercially available from one source only, at the unaffordable price of 1,840€/mg.<sup>[178]</sup>

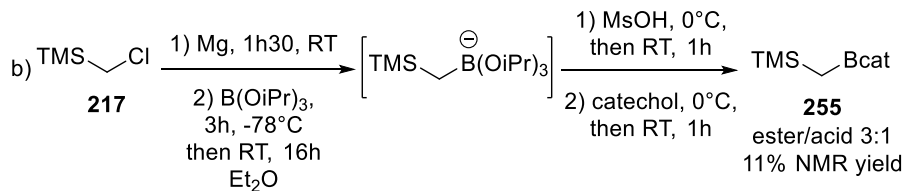
The instability of the catecholboronate should also be noted. The product would start to hydrolyze after a night in the fridge, even under inert atmosphere. To illustrate this, the batch of **255** obtained in the reaction described in **Scheme 101**, d (*vide infra*) was put in solution in diethyl ether, and an aqueous extraction was performed. After separation and concentration of the organic phase, 68% of the initial catechol ester was hydrolyzed and gave the corresponding boronic acid **218** and free catechol (**Scheme 99**). Considering the instability of compound **255**, it was deemed incompatible with aqueous work up and column chromatography. In consequence, we valued a high purity of the crude mixtures obtained in our tests above any other considerations.



**Scheme 99:** Hydrolysis of catecholboronate **255** after an aqueous work-up, measured by  $^1\text{H}$  NMR.

This observation confirmed the unlikeliness of the esterification of boronic acid **218** with catechol. Instead, we proposed the transesterification of a boronate intermediate generated *in situ* from a Grignard reagent. While previously we were hydrolyzing this intermediate to yield the corresponding boronic acid, in these instances we followed a procedure by Matteson and Michnick and added the adequate diol.<sup>[179]</sup> This protocol will be discussed more in-depth later in this thesis (see **Table 26**, page 177). The reaction showed promising results in the formation of Bpin derivative **122**, with an ester/acid ratio of 7:1 (**Scheme 100**, a). Logically, we swapped the diol for catechol in order to synthesize **255** (**Scheme 100**, b). Unfortunately, the ester/acid ratio dropped to 3:1, and the NMR yield, measured using DMT as an internal standard, was only 11%. A significant amount of catechol is also present in the crude, which elimination would be problematic considering the incompatibility of **255** with most common purification methods.

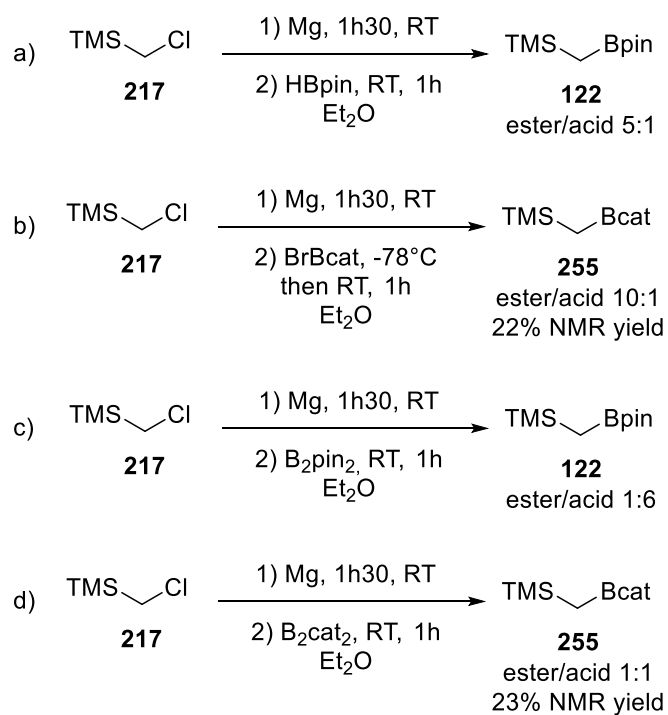




**Scheme 100:** *In situ* transesterification of a boronate with (a) pinacol and (b) catechol.

Considering the challenges of an *in situ* transesterification, we turned our attention to boron reagent already bearing a Bcat group. The reaction with borane HBpin **60** was reported above (see **Table 12, Entry 1**, page 118) with an ester/acid ratio of 5:1 (**Scheme 101, a**). As the catechol equivalent, HBcat **59**, was not available in our lab, we instead used the brominated equivalent BrBcat, already used during our work on the boryl-Heck reaction (see chapter 3.2.2., page 54). To compensate for the higher reactivity of BrBcat relative to its borane counterpart, the addition was carried out at low temperature (**Scheme 101, b**). We were satisfied to observe an improved ester/acid ratio of 10:1, and an NMR yield of 22%. However, the crude mixture was once again contaminated by catechol.

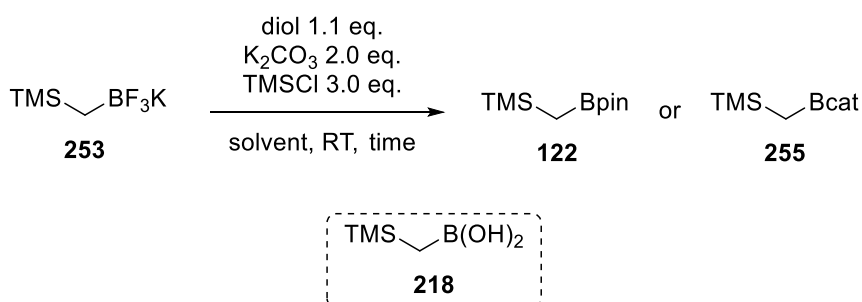
As an alternative, the bis(catecholato)diboron B<sub>2</sub>cat<sub>2</sub> might fill our need. The pinacol equivalent, using B<sub>2</sub>pin<sub>2</sub>, was already tested (see **Table 12, Entry 2**, page 118), resulting in a disappointing ester/acid ratio of 1:6 (**Scheme 101, c**). The higher reactivity of the B<sub>2</sub>cat<sub>2</sub> boosted the ester/acid ratio of 1:1 (**Scheme 101, d**). Although the 23% yield is decent, the amount of boronic ester (and free catechol) in the crude mixture cannot be overlooked.



**Scheme 101:** *In situ* borylation using (a) HBpin, (b) BrBcat, (c) B<sub>2</sub>pin<sub>2</sub>, and (d) B<sub>2</sub>cat<sub>2</sub>.

The esterification of trifluoroborate **253** is another route we explored to form **255**. This type of defluorination process was described earlier in this thesis (**Scheme 65**, page 89).<sup>[148]</sup> Once more, we first tested the feasibility of this strategy using pinacol (**Table 14**).

**Table 14:** Synthesis of the Bcat derivative *via* a defluorination process.



| Entry | diol     | solvent  | Time (h) | Result <sup>a</sup>  |
|-------|----------|----------|----------|----------------------|
| 1     | pinacol  | MeCN     | 2        | <b>218/122</b> 1 : 4 |
| 2     | pinacol  | DMF      | 2        | <b>218/122</b> 5 : 1 |
| 3     | pinacol  | Dry MeCN | 2        | <b>218/122</b> 1 : 4 |
| 4     | pinacol  | acetone  | 2        | <b>122</b> , 13%     |
| 5     | pinacol  | acetone  | 16       | <b>122</b> , 40%     |
| 6     | catechol | acetone  | 16       | <b>255</b> , 23%     |

*a. Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard.*

Our first attempt replicated the reported reaction conditions (**Table 14, Entry 1**).<sup>[148]</sup> A low amount of crude was recovered, in which the desired ester was observed, as a 4 : 1 mixture with the boronic acid **218**. The starting trifluoroborate **253** proved complicated to solubilize in acetonitrile, so the solvent was switched to DMF (**Table 14, Entry 2**). Only traces of **122** were observed, the main component of the crude mixture being the boronic acid.

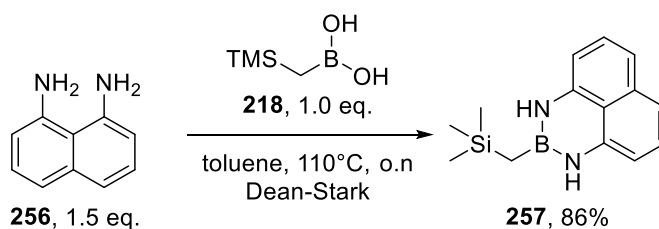
In the absence of an aqueous work up the origin of this hydrolysis was attributed to traces of water in the solvent. Consequently, the reaction was carried out in dry acetonitrile (**Table 14, Entry 3**), without any noticeable variation of the hydrolysis proportion.

The use of acetone allowed for a better dissolution of the starting materials and reduced the amount of hydrolysis to mere traces (**Table 14, Entry 4**). At the end of the reaction, the acetone was evaporated, and the residue was washed with DCM. The concentration under reduced pressure of this organic solution gave **122** in 13% yield. More interestingly, while the yield is very low, the product is perfectly pure. An extended reaction time improved the yield (**Table 14, Entry 5**).

This protocol was applied to the synthesis of the Bcat derivative (**Table 14, Entry 6**). Desired product **255** was obtained in 23% yield, but more importantly, in a pure form, allowing for its use in a subsequent Peterson reaction.

#### 5.2.3.3. BDAN derivatives

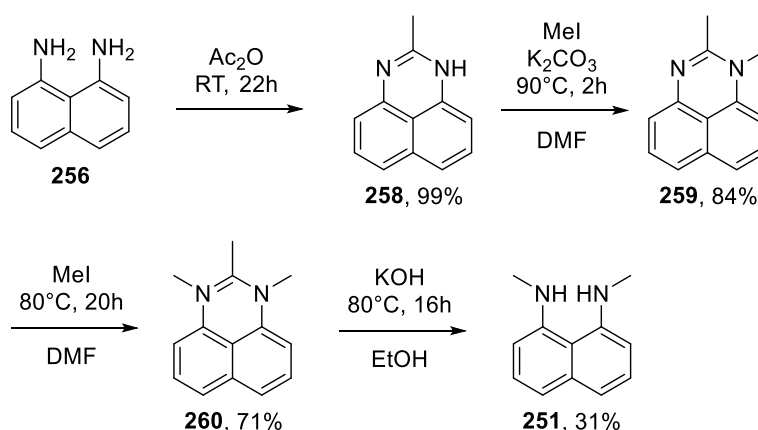
The direct esterification of boronic acid **218**, unsuited for the formation of a Bpin group (see **Table 11**, page 116), was successfully applied when 1,8-diaminonaphthalene (DAN) **256** was used (**Scheme 102**). We reasoned that the improved stability of the BDAN group compared to its Bpin counterpart is at the origin of this difference in reactivity. A purification by column chromatography gave **257** with a 56% yield. Considering that the main impurity is the excess DAN **256**, a succession of acidic and basic washing was done to afford **257**, purer and in a 86% yield.



**Scheme 102:** esterification of boronic acid **218** with DAN.

For reasons discussed below (see **Table 17**, page 147), we were also interested in the N,N'-bismethylated equivalent of **257**. We foresaw that the direct methylation of **257** would give rise to selectivity issue between the mono- and dimethylated products, expected to be challenging to separate from one another.

To circumvent this issue, we chose to methylate the amine **256** before the esterification step. A synthetic route has been reported by Grenz *et al.*<sup>[180]</sup> It consisted in a protection step to yield **258**, followed by two selective methylations to afford **260**, and finally a deprotection step to give the desired MDAN **261** (**Scheme 103**). However, our attempts to replicate those experiments faced multiple difficulties.



**Scheme 103:** Reported synthetic sequence toward *N,N'*-dimethyldiaminonaphthalene (MDAN) **261**.

The first reaction of the series is very simple to put in motion, but the treatment proved to be extremely messy. The acetic anhydride, used in large excess as a solvent, is quenched when the crude is poured onto distilled water. Product **258** supposedly precipitates in water, but this was not observed. We postulated that the acetic acid, resulting from the hydrolysis of the acetic anhydride, reacted with the protected amine **258** to form a soluble salt **262** (**Figure 25**).

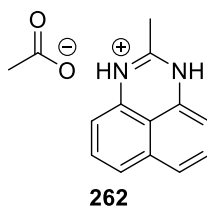


**Figure 25:** postulated ionic product **262**.

We treated the crude mixture with a basic solution until a precipitate appeared. The greenish solid was analyzed by  $^1\text{H}$  NMR and matched the description reported in the literature for **258** (**Figure 26**, bottom). However, a strong signal corresponding to an acetate group was observed too. The next batch of **258** we synthesized was treated more thoroughly, and a yellow solid was obtained. The NMR spectra of this product differed from the previous one with sharper signals, and no acetate present (**Figure 26**, top). We concluded that the description reported by Grenz *et al.* corresponds to the acetate salt **262**.



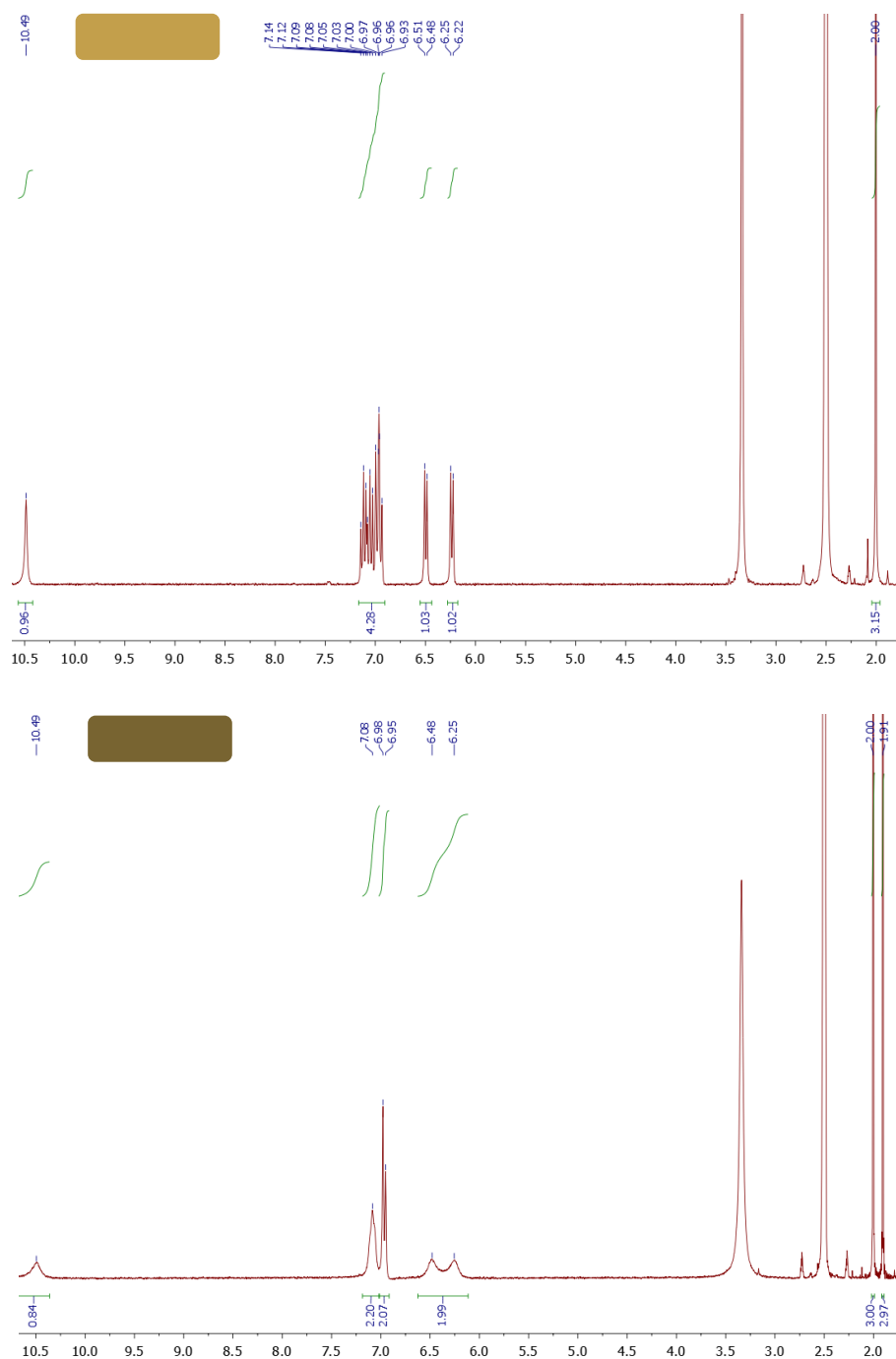
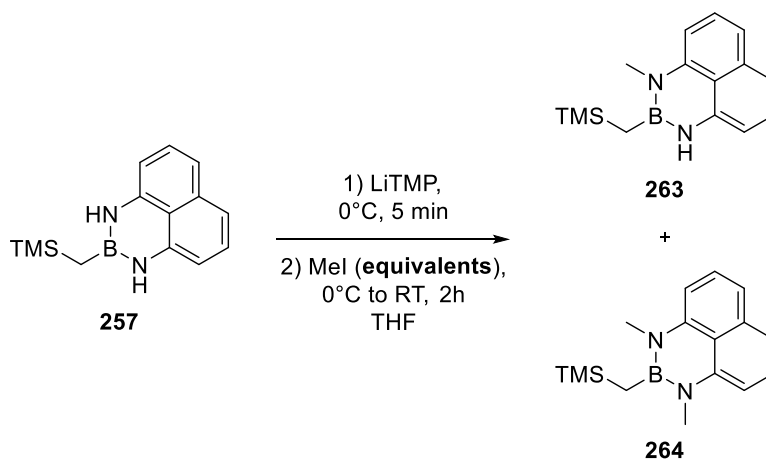


**Figure 26:** Aspect and  $^1\text{H}$  NMR spectra of **258** (yellow, top) and **262** (green, bottom).

Both the pure amine **258** and the acetate salt **262** were put in reaction following the conditions of the second step of the sequence, but in each cases the reaction failed. Consequently, we abandoned this synthetic route and focused instead on the direct methylation of BDAN derivative **257**, despite the anticipated selectivity issue (**Table 15**).

**Table 15:** Methylation of the BDAN derivative.



| Entry          | MeI eq. | Ratio 257/263/264 |
|----------------|---------|-------------------|
| 1              | 1.1     | 2.70 : 2.60 : 1   |
| 2              | 2.2     | 0.20 : 0.35 : 1   |
| 3              | 3.3     | 0.10 : 0.20 : 1   |
| 4              | 4.5     | 0.10 : 0.20 : 1   |
| 5 <sup>a</sup> | 3.3     | 0.30 : 0.50 : 1   |

*a. 4 hours of reaction for the second step.*

Our first experiment was meant to verify if the monomethylated product **263** could be obtained selectively (**Table 15, Entry 1**). A significant amount of dimethylated amine **264** was formed, and, logically, the 1.1 equivalent of MeI was not sufficient to convert all of the starting **257**.

In view of this result, the quantity of methyl iodide was increased to 2.2 equivalents, which led to a crude mixture mainly made of the desired



**264 (Table 15, Entry 2).** The proportion of dimethylated amine was even more favorable when 3.3 equivalents of MeI were used (**Table 15, Entry 3**). Augmenting further the amount of the methylation agent did not modify to outcome of the reaction (**Table 15, Entry 4**).

A longer methylation time was tested to maximize even more the proportion of dimethylated product, but surprisingly yielded a worst crude (**Table 15, Entry 5**).

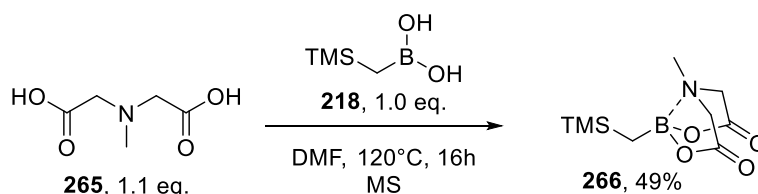
With the reaction conditions described in **Entry 3**, the monomethylated product **263** and the free amine **257** were avoided as much as possible, and the difficult separation of these impurities began. As an illustration, the **Figure 27** represents the TLC done to monitor the advancement of a purification attempt *via* column chromatography. The silica plate was eluted three times in hexane for a better visualization. Interestingly, the various compounds of the crude are readily oxidized after a few minutes upon contact with air. This led to colorful spots, facilitating the identification of the molecules. With practice, this purification afforded the desired BMDAN product in 85% yield.



**Figure 27:** Monitoring the separation of **264** (green-blue, top spot) from **263** (blue, middle spot) and **257** (purple, bottom spot).

#### 5.2.3.4. BMIDA derivatives

The direct esterification of boronic acid **218** was also efficient when *N*-methyliminodiacetic acid (MIDA) **265** was used (**Scheme 104**). However, few adjustments had to be made compare to the synthesis of the BDAN derivative **257**. As the amino acid **265** is not soluble in toluene, DMF was used as the solvent instead. Since this solvent would mix with the water eliminated during the reaction, the Dean-Stark apparatus would be impractical. It was replaced by 4 Å molecular sieves placed directly in the flask. The pure BMIDA derivative **266** was obtained in 49% yield, after a simple precipitation in diethyl ether.



**Scheme 104:** esterification of boronic acid leading to **266**.

We were also interested in the synthesis of the BMDEA derivative **267**, equivalent to the MIDA but without the carbonyl functions. The reaction in DMF, following the conditions that successfully led to **266**, allowed for the formation of the desired **267**, but the crude was contaminated by a significant amount of residual DMF (**Table 16, Entry 1**). The common method to get rid of high boiling point, water-miscible solvent such as DMF is to carry out liquid/liquid extractions using sufficient amount of water. While this strategy efficiently removed the DMF from the organic phase, it also extracted our borylated compound **267**. Alternative solvents were considered to take over from the problematic DMF (**Table 16**).

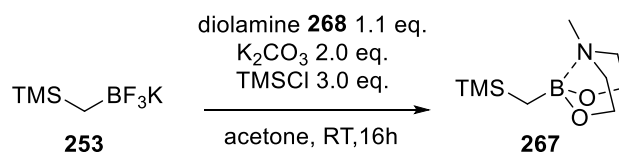
**Table 16:** Esterification of boronic acid **218** using MDEA **268**.

| <p>Reaction scheme: <b>268</b> (1.1 eq.) + <b>218</b> (1.0 eq.) <math>\xrightarrow[\text{desiccant}]{\text{solvent, T}^\circ\text{C, 16h}}</math> <b>267</b></p> |                    |     |                   |                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----|-------------------|------------------|
| Entry                                                                                                                                                            | Solvent            | T°C | Desiccant         | Result           |
| 1                                                                                                                                                                | DMF                | 120 | MS                | <b>267</b> + DMF |
| 2                                                                                                                                                                | toluene            | 110 | Dean-Stark        | Insoluble        |
| 3                                                                                                                                                                | acetone            | 85  | MgSO <sub>4</sub> | <b>218</b>       |
| 4                                                                                                                                                                | CF <sub>3</sub> Ph | 110 | MS                | <b>218</b>       |
| 5                                                                                                                                                                | <i>i</i> PrOH      | 70  | /                 | <b>218</b>       |

As the starting *N*-methyldiethanolamine (MDEA, **268**) was not soluble in toluene, the conditions used for the synthesis of the BDAN derivative **258** could not be tested (**Table 16, Entry 2**). More polar solvent such as acetone (**Table 16, Entry 3**) and trifluorotoluene (**Table 16, Entry 4**) were tested, but only the boronic acid was recovered (the diolamine is presumably eliminated during the aqueous work-up).

A reaction in *isopropanol* was carried out (**Table 16, Entry 5**). We hypothesized that this alcohol would have an active role in the esterification process by attacking the boron center and, hopefully, encouraging the elimination of water. Regrettably, no conversion of the starting boronic acid was observed.

The method based on the defluorination of a trifluoroborate **253**, which fruitfully provided us with the Bpin **122** and Bcat **255** derivatives in low yields but excellent purity, was tested with the diolamine **268** (**Scheme 105**). Unfortunately, the hydrolysis of the starting trifluoroborate and the consequential formation of boronic acid **218** was the only result of this reaction.



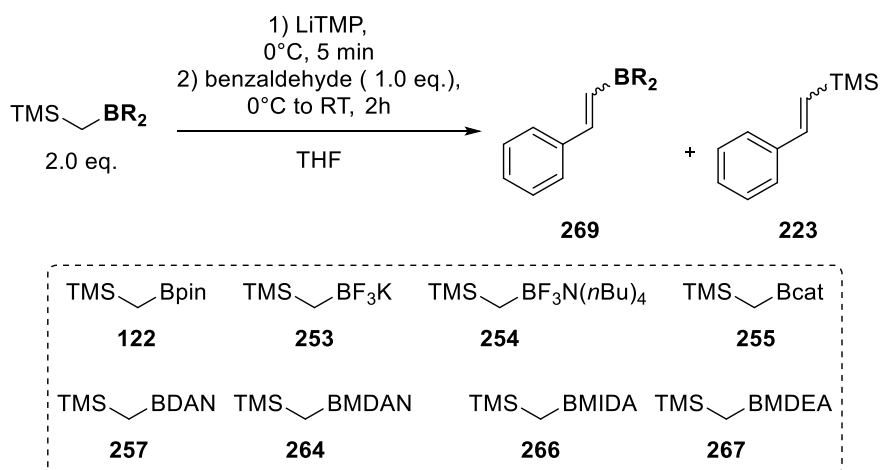
**Scheme 105:** Synthesis of **265** via the defluorination method.

Lacking better conditions, we focused on the esterification in DMF reported in **Table 16, Entry 1**. Rather than washing the DMF away with water, we decided to distill it off. The heating was maintained until the residue turned solid. A dissolution in DCM followed by a precipitation with hexane allowed for the impurities to be filtered out and gave **267** in 45% yield.

#### 5.2.3.5. Olefination assessments

With this library of new *gem*-borylsilylmethanes, we explored the influence of the borylated group's nature on the Peterson/boron-Wittig chemoselectivity (**Table 17**). The reaction conditions we optimized for the olefination of benzaldehyde were used in all the experiments. The successful reaction using our reference Bpin reagent is reported in **Table 17, Entry 1**.

**Table 17:** Influence of the borylated group on the Peterson olefination process.



| Entry | Substrate | Yield <sup>a</sup> 267 (%) | Yield <sup>a</sup> 223 (%) |
|-------|-----------|----------------------------|----------------------------|
| 1     | 122       | 56                         | 0                          |
| 2     | 253       | 0                          | 0                          |
| 3     | 254       | 0                          | 0                          |
| 4     | 255       | 0                          | >1%                        |
| 5     | 257       | 0                          | 0                          |
| 6     | 264       | 0                          | 0                          |
| 7     | 266       | 0                          | 0                          |
| 8     | 267       | 0                          | 0                          |

*a.* Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard.

The trifluoroborate **253** proved insoluble in THF (**Table 17, Entry 2**). This incited use to replace the potassium counter-cation by an organic one, which resulted in the synthesis of **254**. Unfortunately, it was not sufficient to dissolve the trifluoroborate in THF (**Table 17, Entry 3**). An alternative procedure in DCM will be discussed below.

The unstable **255** has to be put in reaction as soon as possible after its synthesis (**Table 17, Entry 4**). While no borylated olefin was detected, an intriguing doublet can be observed at 5.87 ppm by  $^1\text{H}$  NMR, with a coupling constant of 14.1 Hz. This could match one of the characteristic signals of the *Z* silylated olefin **223**, reported at 5.84 ppm with a 15.0 Hz coupling constant.<sup>[181]</sup> This compound was only present in traces however, which does not allow us to confirm its nature through further analyses.

The reagent **257** was recovered after being used in the olefination reaction (**Table 17, Entry 5**). A second BDAN species is observed by  $^1\text{H}$  NMR. Although this side-product's structure was not determined, we suspected that it emanated from the competitive deprotonation of the amine, instead of the central carbon (**Figure 28**, left). We envisioned that the methylation of the amine functions would efficiently prevent this side-reaction. The synthesis of dimethylated **264** confirmed the preferred deprotonation of the amine function rather than the central carbon, as no C-methylation was observed. This new *gem*-borylsilylmethane was involved in an olefination reaction, but it was recovered unreacted in the crude mixture (**Table 17, Entry 6**). We hypothesized that the presence of the methyl groups creates a steric clash with bulky LiTMP, preventing its approach and the subsequent deprotonation. A deprotonation using a small and non-nucleophilic hydride will be discussed below.

The reaction between deprotonated BMIDA reagent **257** and benzaldehyde led to nothing but degradation (**Table 17, Entry 7**). It was surprising that not even the borylated reagent was recovered, considering the high stability of the BMIDA group. Once again, a regioselectivity issue during the deprotonation stage may explain this result, as the protons in  $\alpha$  positions of the carbonyl groups exhibit some acidity (**Figure 28**, right). To tackle this issue, the carbonyl-free BMDEA compound **267** was synthesized. When the olefination reaction was conducted using this reagent, the only noticeable molecule observed in the  $^1\text{H}$  NMR analysis of the crude mixture was the boronic acid **218** (**Table 17, Entry 8**). This result indicated that while the *gem*-borylsilylmethane was inert towards the olefination process, it hydrolyzed under these conditions.

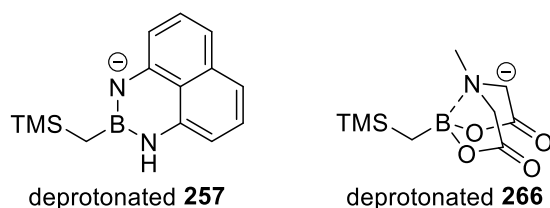
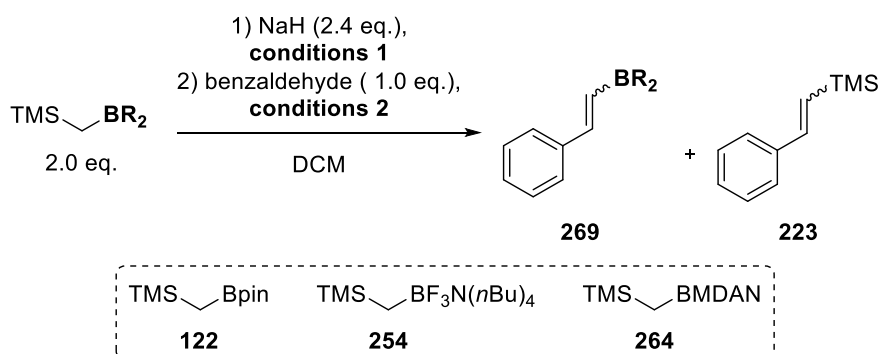


**Figure 28:** competitive deprotonation of **257** (left) and **266** (right).

As discussed above, the ammonium trifluoroborate reagent **254** proved insoluble in THF (**Table 17, Entry 3**). We were interested in carrying out the olefination reaction in DCM as this solvent is able to dissolve our *gem*-borylsilylmethane. However, DCM is not inert for reactions involving organolithium species.<sup>[182]</sup> We thus considered instead the use of sodium hydride NaH as a non-nucleophilic strong base. The small size of the hydride anion could also allow for the deprotonation of **264**, for which the bulkiness of LiTMP could be an issue (**Table 17, Entry 6**). The compatibility of DCM and NaH with our olefination process was first examined using our reference TMS/Bpin reagent **122** (**Table 18, entries 1-3**).

**Table 18:** Peterson olefination attempts using NaH as a base.



| Entry | Substrate  | Conditions 1 | Conditions 2        | Result            |
|-------|------------|--------------|---------------------|-------------------|
| 1     | <b>122</b> | 0°C, 5 min   | 0°C then RT, 2h     | Benzyl alcohol    |
| 2     | <b>122</b> | 0°C, 45 min  | 0°C then RT, 2h     | Benzyl alcohol    |
| 3     | <b>122</b> | -78°C, 1h    | -78°C then RT, 2h30 | Benzyl alcohol    |
| 4     | <b>254</b> | 0°C, 5 min   | 0°C then RT, 2h     | Reagent recovered |
| 5     | <b>264</b> | 0°C, 5 min   | 0°C then RT, 2h     | Reagent recovered |

The first conditions we tried were similar to the THF/LiTMP ones: a temperature of 0°C maintained during the deprotonation and the addition, before a slow warm up to room temperature over two hours to favor the elimination process (**Table 18, Entry 1**). The main constituent of the crude mixture was not the desired borylated olefin **269**, nor even the silylated one **223**, but benzyl alcohol. This side-product, already observed during the optimization we reported earlier (see **Table 1**, page 55), resulted from the reduction of the benzaldehyde. This suggests that hydride, combined with the boron atom, served as a reducing agent and not as a base.

More time was granted to the deprotonation step to proceed, before adding the aldehyde (**Table 18, Entry 2**). In parallel, the reaction was carried out at lower temperatures (**Table 18, Entry 3**). Neither of these initiatives showed signs of the successful deprotonation of the borylated



reagent, and benzyl alcohol was in each case the main product. These results illustrated the inaptitude of sodium hydride to form the necessary carbanion.

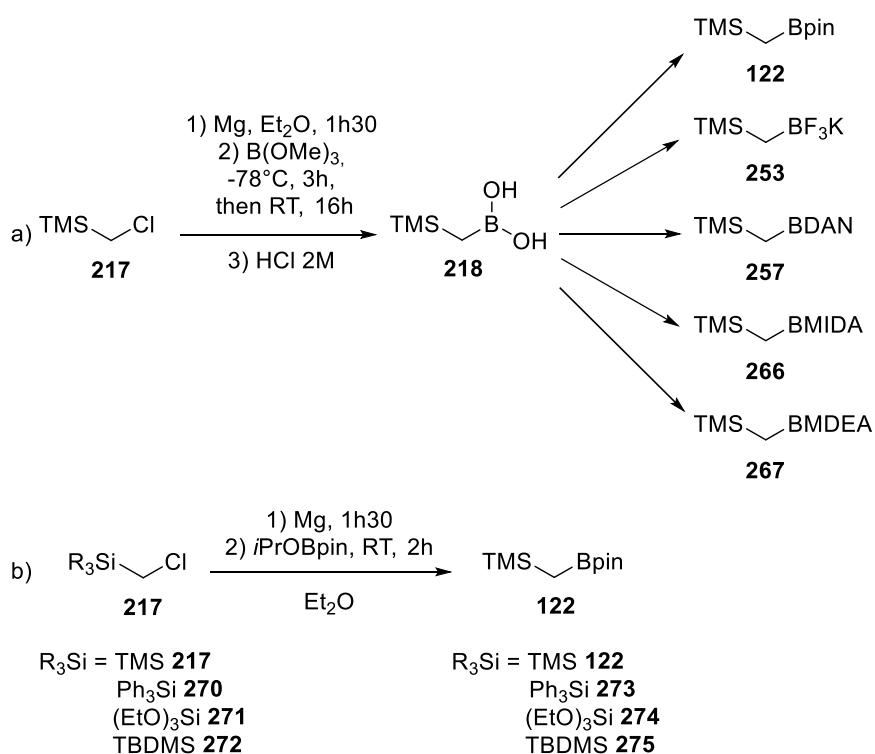
Ammonium trifluoroborate **254** and dimethylated BDAN **264** were expected to be even more difficult to deprotonate. Nevertheless, the reaction was tested with these *gem*-borylsilylmethanes (**Table 18, Entry 4-5**). In both cases, the crude mixture was mainly showing the signals corresponding to the starting *gem*-borylsilylmethane, as anticipated. However, no benzyl alcohol was detected, which could indicate that an electrophilic boron atom is needed for the reduction to occur.

Our exploration of the nature of the boron group demonstrated that the pinacol boronate is not only the best, but also the only boron moiety suited for the synthesis of vinylboronates *via* a Peterson olefination. The more electron rich borylated groups all gave rise to issues pertaining to solubility, regioselectivity of the deprotonation, or excessive pKa of the central proton. The Bcat group was the only one more electrophilic than our Bpin reference, and while this group may have led to the formation of a silylated olefin, only traces of this potential product were detected, which did not allow us to claim its indisputable identification. Such evidence would have been a compelling support of the influence of the boron group electrophilicity over the Peterson/boron-Wittig chemoselectivity.

#### 5.2.4. Nature of the silyl group

Analogously to the boryl moiety, the nature of the silyl group could influence the outcome of an olefination reaction using *gem*-borylsilylmethanes. We were interested in the synthesis of such reagents for which the silicon group would exhibit various electronic and steric properties.

While the syntheses of the numerous borylated groups could be envisioned as a diverging approach from a common boronic acid precursor **218**, each and every silicon substitution would require to perform the Grignard reaction from the corresponding  $\alpha$ -halogenosilane **217**, **270-272** (**Scheme 106**).

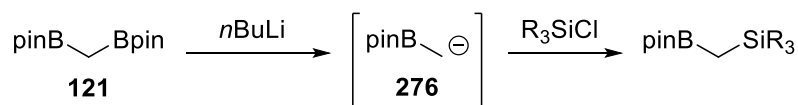


**Scheme 106:** (a) The divergent strategy for the boron group variation opposed to (b) the linear strategy for the silyl group variation.

Consequently, another synthetic method was considered for these compounds, based on the deborylation of *gem*-bisborylmethane **121**.

#### 5.2.4.1. Deborylation-silylation sequence

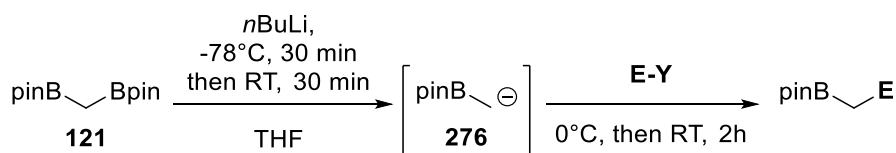
During our work on the boron-Wittig, we mentioned that the *gem*-bisborylmethane **121** must be deprotonated using a strong and bulky base such as LiTMP (see **Figure 7**, page 39).<sup>[119]</sup> When methyllithium or butyllithium were used instead, they formed an ate complex which triggered a deborylation process (see **Scheme 38-39**, page 38).<sup>[116-117]</sup> Therefore, we designed a divergent synthesis of various *gem*-silylborylmethanes from a common precursor, the *gem*-bisborylmethane **121** (see chapter 4.1., page 63 for its synthesis) (**Scheme 107**).



**Scheme 107:** The divergent strategy based on the deborylation of *gem*-bisborylmethane **121**.

We initiated this work using TBDMSCl and Ph<sub>3</sub>SiCl as the electrophile, more studies were later carried out using TMSCl, MeI and MeOD (**Table 19**).

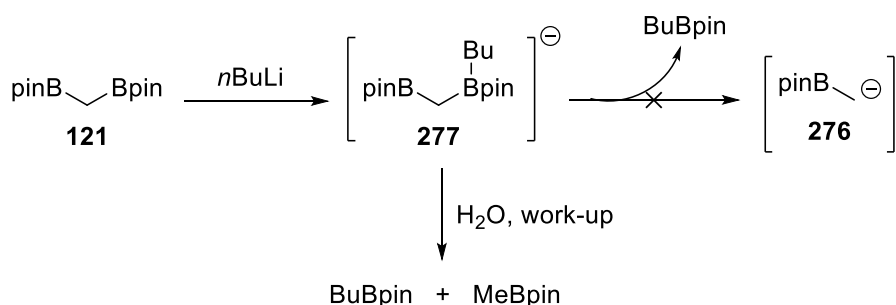
**Table 19:** Functionalization of **121** *via* deborylation.



| Entry | E-Y                  | Result                      |
|-------|----------------------|-----------------------------|
| 1     | TBDMSCl              | <b>121</b> , BuBpin, MeBpin |
| 2     | Ph <sub>3</sub> SiCl | <b>121</b> , BuBpin, MeBpin |
| 3     | TMSCl                | <b>121</b> , BuBpin, MeBpin |
| 4     | MeI                  | <b>121</b> , BuBpin, MeBpin |
| 5     | MeOD                 | <b>121</b> , BuBpin, MeBpin |

We first focus on the synthesis of **275** and **273** using TBDMSCl and Ph<sub>3</sub>SiCl respectively as electrophiles (**Table 19**, **Entry 1-2**). The expected *gem*-silylborylmethanes were not obtained, the main constituents of the crude mixture being the starting **121**, MeBpin, and BuBpin. It is conceivable that the three phenyl groups of Ph<sub>3</sub>SiCl or the tertbutyl group of TBDMSCl created a steric hindrance such that it prevents the attack of **276**. To exclude this possibility, control experiments were done using TMSCl, MeI and MeOD as electrophiles (**Table 19**, **Entry 3-5**). None of the corresponding products were obtained, and the crude were identical in all cases.

The outcome of the reaction is independent of the nature of the electrophiles involved. The formation of butylpinacolboronate during the process indicates the good addition of *n*BuLi on the boron group. However, it seems that the deborylation of the so-formed ate complex **277** did not occur *in situ*. As a result, the carbanion **276** is not formed in the reaction medium and available to perform the subsequent S<sub>N</sub>2 reaction. The complex **277** was preserved during the whole process, and eventually hydrolyzed upon quenching with water, which released both BuBpin and MeBpin (**Scheme 108**).



**Scheme 108:** Instability of carbanion **276** and hydrolysis of complex **277**.

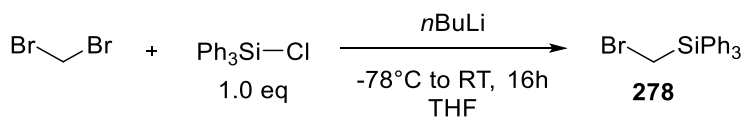
In view of these results, we reconsidered the Grignard route for the synthesis of new *gem*-silylborylmethanes.

#### 5.2.4.2. Synthesis of $\alpha$ -halogenosilane precursors

The formation of a Grignard reagent requires first to have access to the corresponding  $\alpha$ -halogenosilane precursors. Unfortunately, few of the commercially available  $\alpha$ -chloro,  $\alpha$ -bromo or  $\alpha$ -iodosilane possessed silylated group exhibiting sought after properties. In consequence, the synthesis of such compounds had to be investigated.

A protocol reported by Pannell and Kobayashi provided a solid base for this work.<sup>[183]</sup> In a Barbier-like procedure, a chlorosilane is mixed with dibromomethane in THF before *n*BuLi is added at a carefully maintained low temperature (**Table 20**).

**Table 20:** Synthesis of **278** using Pannell's approach.



| Entry          | CH <sub>2</sub> Br <sub>2</sub> eq. | Conditions                           | CH <sub>2</sub> signal <sup>b</sup> | Arom. integration <sup>b</sup> |
|----------------|-------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|
| 1              | 1.0                                 | <i>n</i> BuLi 1.0 eq                 | 3.20 ppm                            | 189 H                          |
| 2              | 1.0                                 | <i>n</i> BuLi 1.0 eq,<br>LiBr 1.5 eq | 3.20 ppm                            | 498 H                          |
| 3              | 4.0                                 | <i>n</i> BuLi 3.0 eq                 | 3.20 ppm                            | 30 H                           |
| 4              | 4.0                                 | <i>i</i> PrMgCl.LiCl<br>3.0 eq       | 3.66 ppm                            | 10 H                           |
| 5              | 1.5                                 | Mg 1.2 eq                            | /                                   | /                              |
| 6 <sup>a</sup> | 4.0                                 | <i>n</i> BuLi 3.0 eq                 | /                                   | /                              |

*a.* TBDMSCl used as the substrate; *b.* measured by <sup>1</sup>H NMR

The conditions reported by Pannell and Kobayashi were tested first (**Table 20, Entry 1**). A singlet corresponding to the desired product **278** was observed at 3.20 ppm on the <sup>1</sup>H NMR spectrum of the crude mixture. When this signal, postulated to represent the protons of the central carbon, was set to integrate for two protons, the integration of the aromatic signals skyrocketed to 189. This discrepancy worsened when lithium bromide, a stabilizer of the BrCH<sub>2</sub>Li intermediate, was added in the reaction medium (**Table 20, Entry 2**).<sup>[184]</sup> The desired bromide **278** is observed, but the conflicting amount of aromatic signals indicated the overwhelming presence of other phenyl compounds, such as the starting chloride.

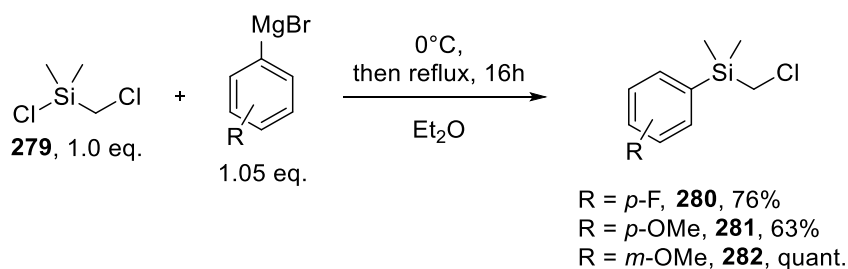
A few additional experiments were necessary to fine-tune the reagents proportions, which resulted in the conditions described in **Table 20, Entry 3**. The integration of the aromatic signals, worth thirty protons instead of the expected fifteen, indicated that **278** could constitute roughly half of the crude mixture. Purifications by column chromatography or recrystallization both failed to yield the isolated α-bromosilane.

In an attempt to generate cleaner, crude mixture, other metalation methods were tested. The use of Turbo Grignard reagent led to the formation of a different unidentified product (**Table 20, Entry 4**), while the Grignard formation using magnesium never started (**Table 20, Entry 5**).

The purification of **278** proved unsuccessful, but the conditions reported in **Table 20, Entry 3** undoubtedly formed the desired product. These conditions were tested on another chlorosilane, TBDMSCl (**Table 20, Entry 6**). Unfortunately, no trace of the corresponding desired product was detected with this substrate.

#### 5.2.4.3. Synthesis and reaction of gem-silylborylmethanes

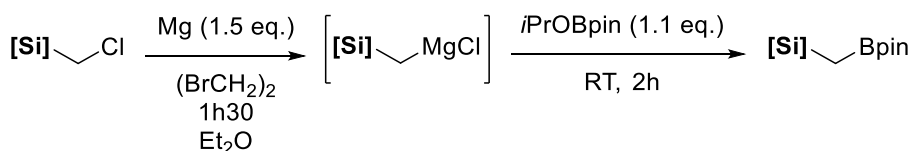
A different synthetic pathway toward  $\alpha$ -chlorosilane was considered. The nucleophilic attack of various commercially available Grignard reagents on (chloromethyl)dimethylchlorosilane **279** was explored.<sup>[185]</sup> After a cautious addition at 0°C, the reaction proceeded at reflux overnight with the regioselective substitution of the chloride borne by the silicon atom (**Scheme 109**). The fluoro derivative **280** and the *para* methoxy derivative **281**, were obtained in good yields after purification, while in contrast the *meta* methoxy derivative was directly obtained in a very clean crude mixture. In the absence of any purification, **282** was obtained in a quantitative yield.



**Scheme 109:** Syntheses of  $\alpha$ -chlorosilanes **280**, **281**, and **282**.

To these three synthesized  $\alpha$ -chlorosilanes, two commercially sourced ones were added, the phenyl derivative **283** (R = H) as well as the triethoxy (EtO)<sub>3</sub>SiCH<sub>2</sub>Cl **284**. The borylation of these compounds was then carried out according to the Grignard procedure that efficiently gave the TMS/Bpin reference reagent **122** (**Table 21**).

**Table 21:** Variation of the silylated group using a Grignard reaction.



| Entry          | Reagent    | [Si]                                                          | Product    | Yield (%) |
|----------------|------------|---------------------------------------------------------------|------------|-----------|
| 1              | <b>283</b> | PhMe <sub>2</sub> Si                                          | <b>285</b> | 31        |
| 2              | <b>280</b> | <i>p</i> -FC <sub>6</sub> H <sub>5</sub> Me <sub>2</sub> Si   | <b>286</b> | 0         |
| 3              | <b>281</b> | <i>p</i> -OMeC <sub>6</sub> H <sub>5</sub> Me <sub>2</sub> Si | <b>287</b> | 81        |
| 4              | <b>282</b> | <i>m</i> -OMeC <sub>6</sub> H <sub>5</sub> Me <sub>2</sub> Si | <b>288</b> | 34        |
| 5              | <b>284</b> | Si(EtO) <sub>3</sub>                                          | <b>289</b> | 0         |
| 6 <sup>a</sup> | <b>284</b> | Si(EtO) <sub>3</sub>                                          | <b>289</b> | 0         |

*a. Barbier conditions, reflux*

The procedure was first tried on the commercially supplied phenyl derivative **283** (Table 21, Entry 1). The desired product **285** was obtained in a low yield but this is mainly due to the purification by column chromatography (as this is often the case with pinacolboronic esters).

In the case of the fluoro derivative **280**, the *in situ* formation of the corresponding Grignard did not start (Table 21, Entry 2). Since the *para*-fluoro phenyl product **286** was not a crucial compound for our chemoselectivity study, the reaction was abandoned after two unsuccessful attempts.

In contrast, the *para*-methoxy derivative **281** was readily converted, and the crude mixture did not require any purification, what explains the high 81% yield in **287** (Table 21, Entry 3). The *meta*-methoxy derivative **282** was also successfully converted but, in this case, the Grignard step proved

extremely reluctant (**Table 21, Entry 4**). Six attempts were carried out before the desired **288** could be obtained, a further testimony of the stubbornness of the Grignard reaction. Nevertheless, the desired product was formed, in a 34% yield after flash chromatography.

The formation of a Grignard intermediate from the triethoxy derivate **284** was reported to be delicate.<sup>[186]</sup> The reaction temperature must be sufficient for the Grignard formation, but low enough to avoid the trimerization observed when a more intense heating is applied (**Scheme 110**). Our first attempt, carried out at room temperature did not show any trace of the Grignard's formation (**Table 21, Entry 5**). To encourage the reaction, we decided to refluxed the mixture. As such high temperatures can result in the trimerization discussed above, the borylating reagent was added initially into the medium in a Barbier-type of procedure, to consume the Grignard reagent as soon as it is formed (**Table 21, Entry 6**). This precaution, however, proved unnecessary as the magnesium remained unreacted.

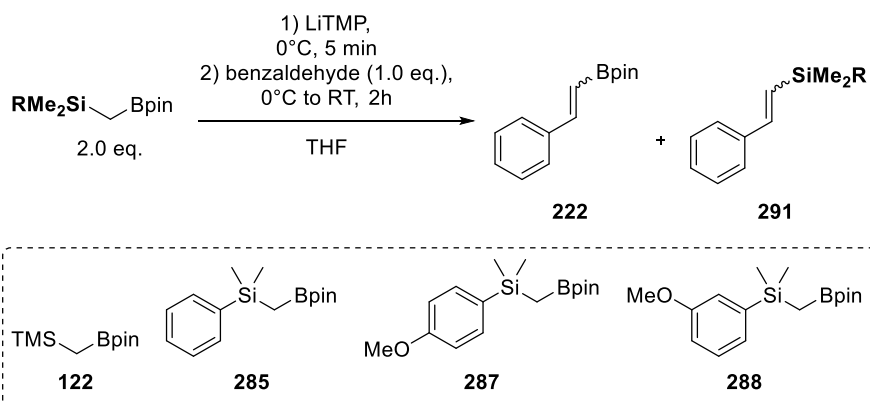


**Scheme 110:** Trapping and trimerization of the triethoxysilyl Grignard by Moreau *et al.*

The three newly synthesized dimethylarylsilyl derivatives **285**, **287**, and **288** were used in an olefination procedure with benzaldehyde (**Table 22**). In all cases, the borylated olefin was obtained as the main product, in a *Z/E* ratio of ca. 2 : 1. For comparative reasons, the results obtained with the reference *gem*-borylsilylmethane **122** are reminded in **Table 22, Entry 1**.



**Table 22:** Influence of the silylated group on the Peterson olefination of benzaldehyde.



| Entry | Reagent    | Yield <sup>a</sup><br>222 Z (%) | Yield <sup>a</sup><br>222 E (%) | Yield <sup>a</sup><br>291 (%) | Chemoselectivity<br>222/291 |
|-------|------------|---------------------------------|---------------------------------|-------------------------------|-----------------------------|
| 1     | <b>122</b> | 36                              | 20                              | 0                             | 100 : 0                     |
| 2     | <b>285</b> | 9                               | 5                               | traces                        | /                           |
| 3     | <b>287</b> | 13                              | 7                               | 2                             | 10 : 1                      |
| 4     | <b>288</b> | 39                              | 20                              | 5                             | 12 : 1                      |

*a. Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard.*

The replacement of one methyl group by a phenyl led to a reduced yield, presumably due to the increased steric hindrance which disfavored the Peterson olefination (**Table 22, Entry 2**). The deactivation of the Peterson pathway by steric effects is probably also why, for the first time, we unambiguously observed traces of the silylated olefin **291**.

Surprisingly, the electron-enriched *para*-methoxy substituted reagent **288** yielded a larger amount of Peterson product, although only marginally (**Table 22, Entry 3**). The yield of the silylated olefin, however, was notably increased.

The *meta*-methoxy substitution of the aryl showed that the steric effect can be compensated by increasing the electrophilicity of the silyl group (**Table 22, Entry 4**). The reaction with **288** led to a yield on par with the one observed using **122**. However, unlike with the reference TMS/Bpin reagent, 5% of the corresponding silylated olefin **291** is also formed.

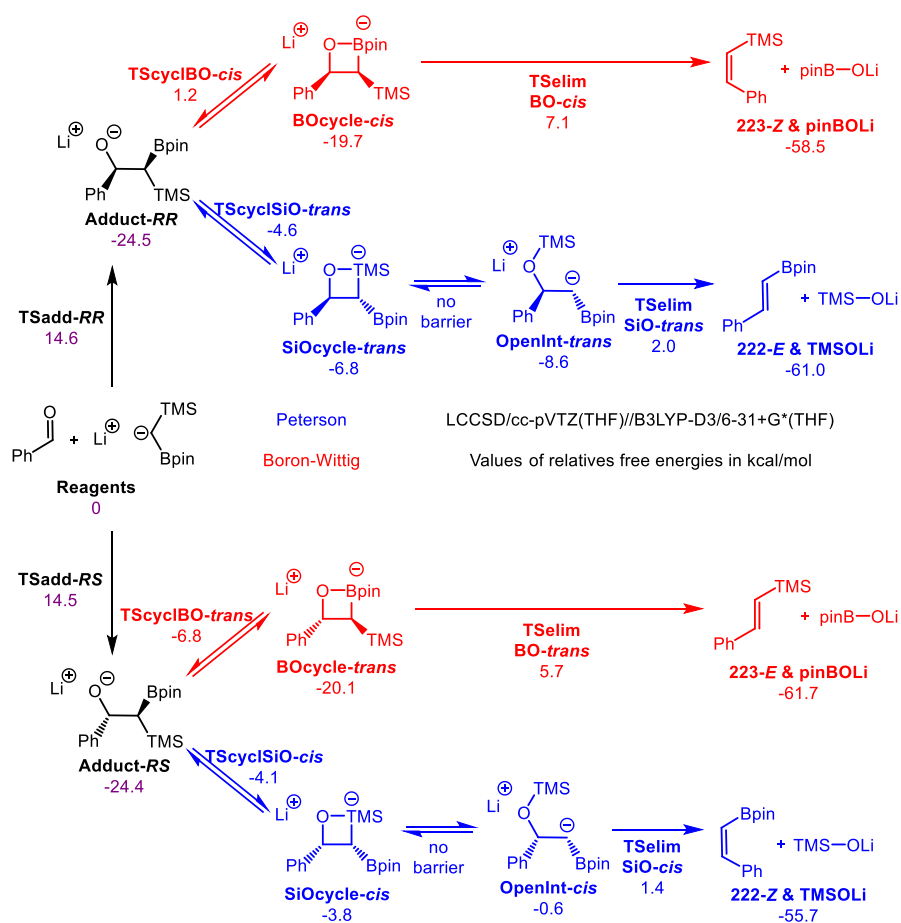
The boron-Wittig/Peterson chemoselectivity was found to be independent on the electronic effect of the silyl group, as both olefination processes appeared equally favored when the donating mesomeric effect of the *para*-methoxy is replaced by the withdrawing inductive effect of the *meta*-methoxy substituent.

In order to support our experimental observations and gain further insights into the factors controlling reactivity, chemoselectivity and stereoselectivity, we conducted a DFT study.

#### 5.2.5. Computational study of the olefination processes

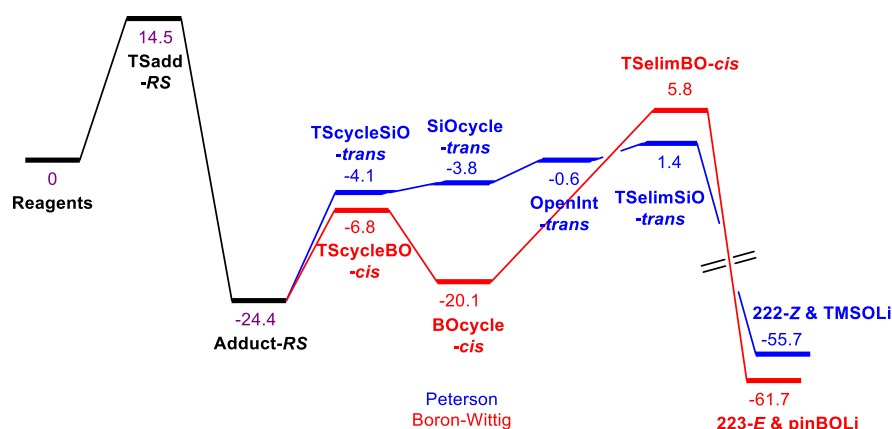
We investigated the reaction by computational means taking deprotonated **122** and benzaldehyde as model substrates. All geometry optimizations were carried out at the B3LYP-D3/6-31+G\*(THF) level of theory (see chapter 9.3.1., page 260 for full details on methods). Frequency calculations were performed to obtain thermal and entropic contributions to free energy. Following a benchmark study (see **Table 35**, page 261 for data), gas phase electronic energies were refined at the LCCSD/cc-pVTZ level.

Both olefination reactions were anticipated to proceed via a similar three steps mechanism: addition, cyclisation and elimination. The addition of the deprotonated TMS/Bpin reagent **122** can occur on either side of the carbonyl group, leading to a pair of diastereomers, **Adduct-*RS*** and **Adduct-*RR***. Each of these isomeric adducts can then undergo cyclisation by attack of the alkoxide moiety on the boron atom (on the way to the boron-Wittig reaction) or on the silicon atom (Peterson pathway). In the case of the Peterson process, elimination was predicted to proceed in two steps via an additional open intermediate (**OpenInt, Scheme 111**).



**Scheme 111:** Mechanism for the competing Peterson and boron-Wittig olefinations through *RR* diastereomer (top) or *RS* diastereomer (bottom).

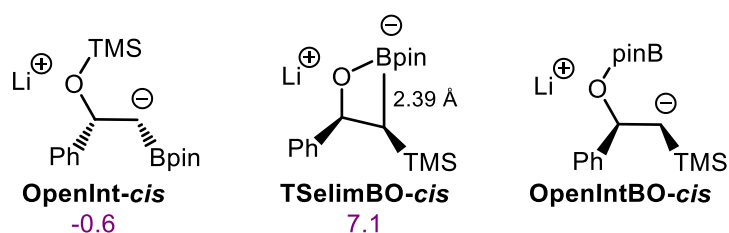
As it was experimentally observed, the major product of this olefination reaction is the *Z* borylated olefin. This compound could be formed only from the *RS* diastereomer, which free energy profile is represented in **Figure 29**.



Computed at the LCCSD/cc-pVTZ(THF)//B3LYP-D3/6-31+G\*(THF) level.

**Figure 29:** Free energy profile (kcal/mol relative to reactants) for the boron-Wittig and the Peterson pathways through the *RS* diastereomer.

Our exploration of the elimination processes put the light on the existence of an additional open intermediate **OpenInt-cis** in the Peterson mechanism, absent in the boron-Wittig reaction (**Figure 30**, left). However, the B-O elimination was predicted to be extremely asynchronous, displaying an elongated B-C bond in the transition state **TSelimBO-cis** (**Figure 30**, center). The intermediate **OpenIntBO-cis** was not found as a local minimum (**Figure 30**, right). This can be justified by the stabilization of the negative charge by the boron group in **OpenInt-cis**, while no such stabilization is possible in **OpenIntBO-cis**. This better stabilization of the developing negative charge could account for the easier elimination from **SiOcycle-cis**, as shown by Aggarwal's studies.<sup>[173]</sup> The highly asynchronous elimination transition state with an advanced C-Si or C-B bond breaking, while the C-O bond remains largely unaffected, could explain why the nature of the carbonyl partner has no influence on chemoselectivity, in contrast to the significant impact of substituents borne by the central carbon revealed by Aggarwal's study.



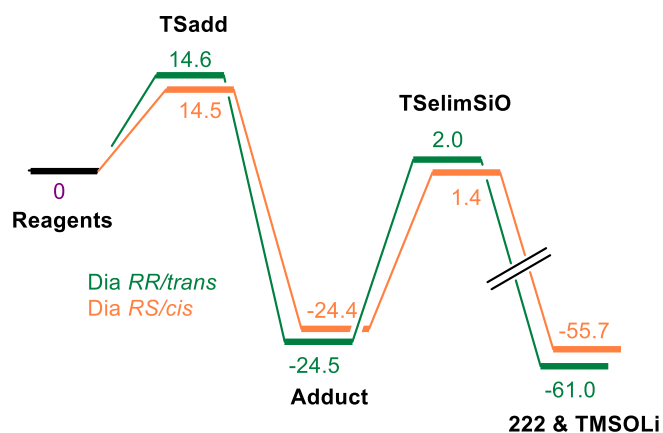
Computed at the LCCSD/cc-pVTZ(THF)//B3LYP-D3/6-31+G\*(THF) level.

**Figure 30:** Intermediate of the Peterson elimination (left), transition state of the boron-Wittig elimination (center), and hypothetical intermediate of the boron-Wittig elimination (right).

#### 5.2.5.1. Origin of the Z/E selectivity

As discussed above, two diastereomers can be formed following the addition of deprotonated **122** on benzaldehyde. Experimentally, only the borylated olefin resulting of the Peterson olefination was obtained and a 2/1 selectivity was observed, in favor of the Z-alkene. Given the predicted non-reversibility of the addition and the stereospecificity of the subsequent steps (*vide infra*), stereoselectivity must be determined at the addition step (**Figure 31**).

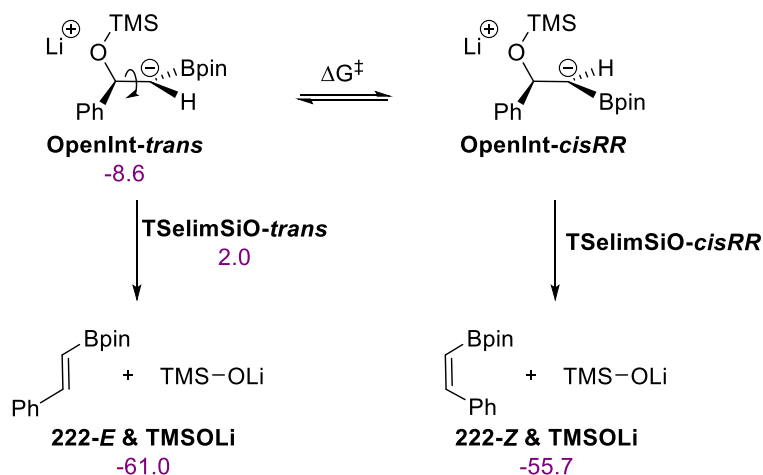
Following the addition step, the *RR* adduct would lead to *E* borylated olefin, and the *RS* adduct to the Z borylated olefin. The computed 0.1 kcal/mol difference in relative free energy between the two diastereomeric addition TS predicts a preferred formation of the *RS* adduct with a very low diastereomeric selectivity. Considering the margin of error inherent to the computational tools, this result matches the experimentally observed 2:1 Z/E ratio.



Computed at the LCCSD/cc-pVTZ(THF)//B3LYP-D3/6-31+G\*(THF) level.

**Figure 31:** Summary of the key steps involved in the *Z/E* selectivity (free energies in kcal/mol).

In order to confirm the stereospecificity of the elimination process, the possibility to operate a rotation around the carbon-carbon single bond of the **OpenInt** intermediate was also considered (**Scheme 112**). Indeed, an equilibrium could be envisaged between **OpenInt-trans** and **OpenInt-cisRR** (not to be confused with **OpenInt-cis**, based on the *RS* isomer). If this equilibrium is faster than (or competitive with) the elimination toward **E-222**, the overall elimination would not be fully stereospecific.



**Scheme 112:** Conceivable *cis/trans* equilibrium (free energies in kcal/mol).

A geometry scan of the rotation was conducted, and the calculated values are gathered in **Figure 32**. The scan revealed that the complete rotation would involve a free energy barrier 8.1 kcal/mol higher than **TSelimSiO-trans**. Accordingly, the elimination step can be considered as fully stereospecific.

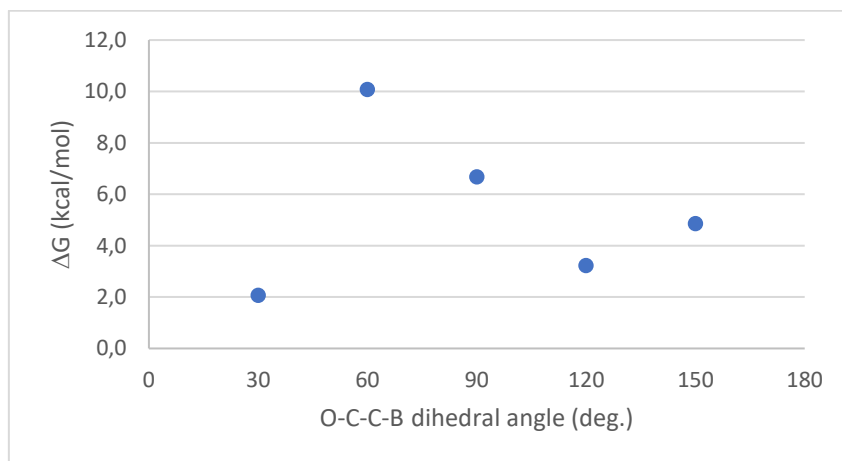


**Figure 32:** Geometry scan at variable O-C-C-B dihedral angles in **OpenInt-trans**, computed at the LCCSD/cc-pVTZ(THF)//B3LYP-D3/6-31+G\*(THF) level.

#### 5.2.5.2. Origin of the boron-Wittig/Peterson chemoselectivity

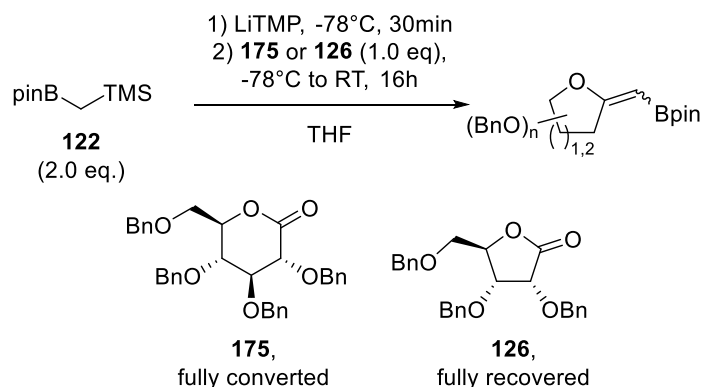
Although several differences could be pointed out between the boron-Wittig and the Peterson olefination processes, both exhibit non-reversibility in the formation of final products, with the elimination step emerging as the chemoselectivity determining step. The free energy barrier for the elimination step in the boron-Wittig pathway is 30.1 kcal/mol, whereas, in the case of the Peterson pathway, it stands at 25.8 kcal/mol (see **Figure 29**). This computed 4.3 kcal/mol difference predicts a total chemoselectivity in favor of the Peterson olefination. This result is in good agreement with the experimental observations showing a complete chemoselectivity toward the vinylboronate formation.

According to the free energy profile (**Figure 29**), the transition state of the elimination to the olefin was found to be the rate determining step of both the boron-Wittig and Peterson pathways. This also explains why the

reactivity is not governed by the electrophilicity of the aldehyde (see **Scheme 95**, page 129), as the addition of the *gem*-borylsilyl carbanion to the aldehyde is not the rate-determining step.

### 5.3. Miscellaneous Peterson olefinations

Our exploration of the boron-Wittig and Peterson olefination reactions led to a more in-depth comprehension of these processes. However, this work was conducted on aldehydes and ketones, and the extension to lactones remained a key step towards our main objective: the synthesis of borylated *exo*-glycal. Since the variation of the silyl and boryl groups did not lead to the identification of an upgraded reagent, the TMS/Bpin reagent **122** was still our most promising candidate. It was therefore used in the Peterson olefination of sugar lactone substrates **175** and **126** (**Scheme 113**).



**Scheme 113:** Peterson reaction on benzyl-protected sugar lactone substrates.

The corresponding borylated *exo*-glycal was not observed in either case. While six-membered ring sugar lactone **175** led to the full conversion of the substrate into a complex mixture, five-membered ring sugar lactone **126** was fully recovered within a clean crude mixture.

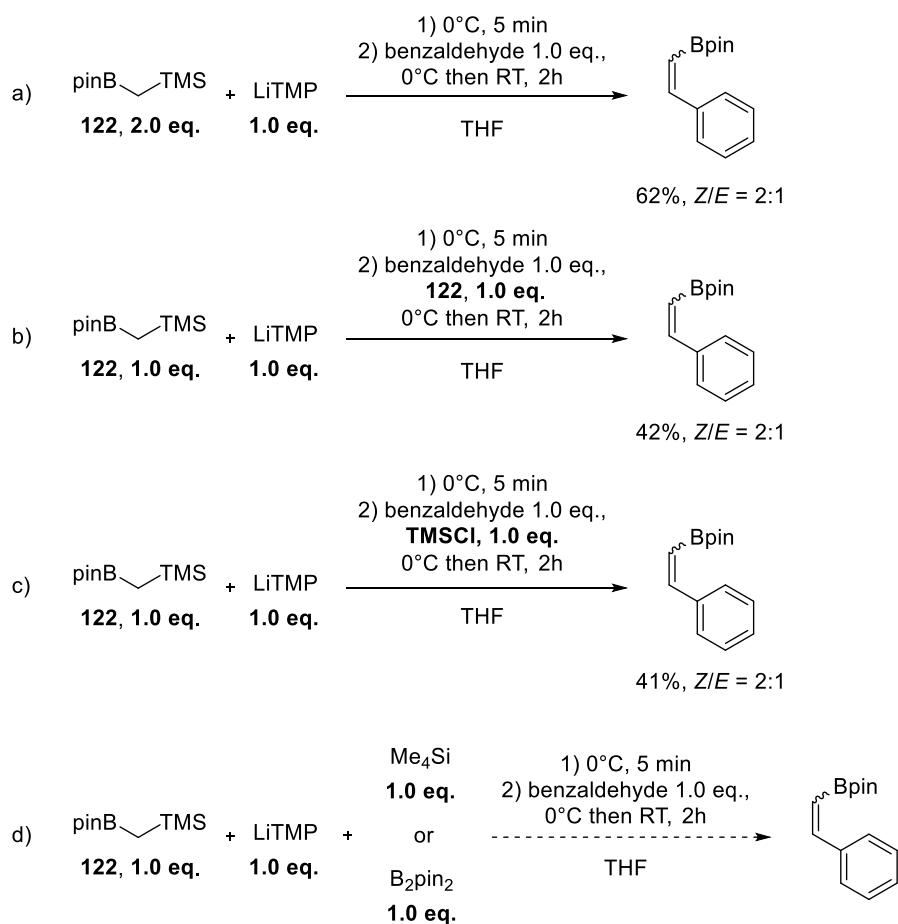
In a further effort to understand the olefination process, the apparent need for two equivalents of *gem*-silylborylmethane intrigued us. Specifically, we were curious to know if the second equivalent of **122** needed to be deprotonated or not. Therefore, we conducted an experiment



with one equivalent of LiTMP, leading to the deprotonation of only half of the *gem*-silylborylmethane **122** (Scheme 114, a). Interestingly, the borylated styrene was formed in yield and isomer selectivity matching what was observed previously when all the reagent was deprotonated. Thus, we reasoned that the beneficial effect brought by the second equivalent of **122** was not linked to the presence of a nucleophilic carbanion.

The source of the advantageous excess of **122** might be correlated to the presence of spare silylated or borylated groups in the reaction medium. For instance, these groups could assist the departure of the TMSOLi moiety by complexing the oxygen. To verify this assertion, the second equivalent of **122** was added to the reaction alongside the benzaldehyde (Scheme 114, b). The yield dropped to the level of the reaction carried out with one equivalent of **122** during our optimization of the reaction conditions (see Table 13, Entry 5, page 122). A similar result was obtained when the second equivalent of **122** was replaced by TMSCl (Scheme 114, c). It would appear that in order to reap the benefit from the second equivalent of *gem*-silylborylmethane, it must be present in the reaction solution from the beginning of the process. For that reason, its influence is probably impacting the deprotonation or addition steps rather than the elimination one.

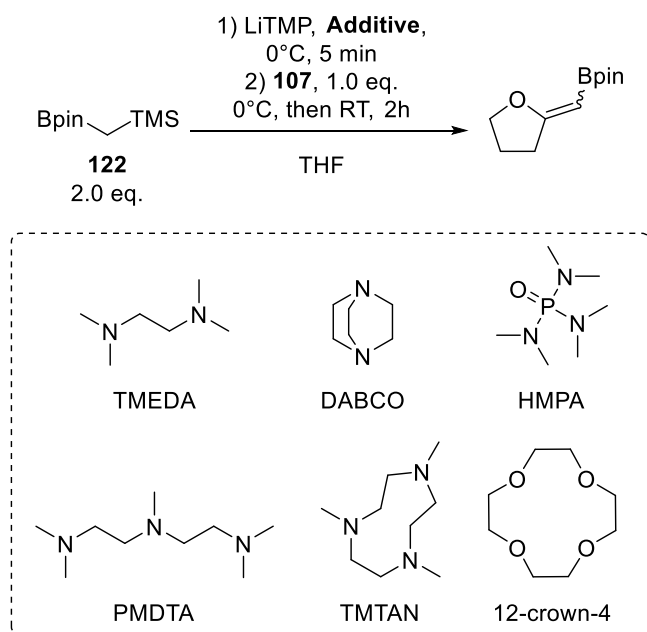
To determine from which of the silylated or borylated group originated the beneficial effect, we designed additional experiments where the second equivalent of **122** was replaced by a silane or a boron compound (Scheme 114, d). Tetramethylsilane and B<sub>2</sub>pin<sub>2</sub> would be good candidates. However, these reactions could not be conducted due to time limitation.



**Scheme 114:** Peterson reaction using only one equivalent of deprotonated **122**.

As it was the case for the boron-Wittig reaction (see **Scheme 58**, page 79), the addition of a nucleophilicity enhancer was envisaged to encourage the reaction. The five membered ring reference lactone **107** was once again chosen as our substrate in reactions using our optimized conditions. On top of the previously used TMEDA and DABCO, we added HMPA and 12-crown-4 ether, commonly used for the capture of lithium cation, as well as PMDTA and TMTAN, which were recently reported for a similar purpose (**Table 23**).<sup>[187]</sup>

**Table 23:** Impact of cation traps on the Peterson olefination outcome.



| Entry | Additive            | Result                                     |
|-------|---------------------|--------------------------------------------|
| 1     | TMEDA 1.0 eq.       | Starting material                          |
| 2     | DABCO, 1.0 eq.      | Unknown side-product <b>292</b> (maj.)     |
| 3     | HMPA, 2.0 eq.       | <b>122</b> + HMPA                          |
| 4     | PMDTA, 1.5 eq.      | Unknown side-product <b>292</b> (maj.)     |
| 5     | TMTAN, 2.0 eq.      | <b>122</b> + TMTAN                         |
| 6     | 12-crown-4, 2.0 eq. | Side-product <b>293</b> , 28% <sup>a</sup> |

*a. Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard.*

The reaction carried out in the presence of TMEDA only led to the recovery of the starting material (**Table 23, Entry 1**). In contrast, an unknown side-product is observed when either DABCO (**Table 23, Entry 2**) or PMDTA (**Table 23, Entry 4**) is used as additives. The <sup>1</sup>H NMR analysis of this side-product **292** showed an open chain structure, not unlike what was

observed during our work on the boron-Wittig reaction (see **Figure 16**, page 76). However, the signals of the newly detected **292** did not match what was found for **153** (**Figure 33**). The borylated group, at the origin of a shielding effect as seen with the 1.58 ppm signal of **153**, is not present in **292**. The exact nature of the Nu moiety resulting from the nucleophilic attack at the origin of the ring-opening is unknown to this day.

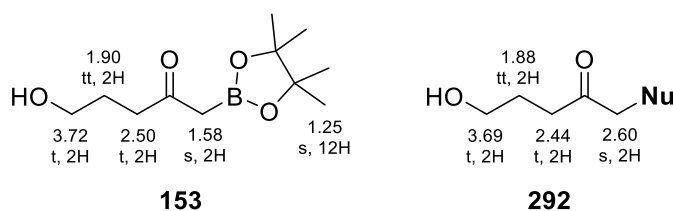


**Figure 33:**  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*) shifts of unknown products **153** and **292**.

The reaction conducted in the presence of HMPA led to its recovery, alongside reagent **122** (**Table 23**, **Entry 3**). A similar result is obtained with TMTAN (**Table 23**, **Entry 5**).

The presence of 12-crown-4 ether in the reaction medium (**Table 23**, **Entry 6**) led to the formation of a new product, identified as a vinylboronate (**Figure 34**). The product was lost when purification on silica (flash chromatography or preparative TLC) was performed. This, combined with the 4.17 ppm signal in  $^1\text{H}$  NMR, too low to be adjacent to a Bpin group, led us to postulate that the product is a boronic acid. The coupling constant of 14.4 Hz indicates a *Z* configuration of the double bond, and no signal that could correspond to its *E* counterpart was found. The high shift of the 4.00 ppm signal, and its absence of further coupling besides the ones with the vinyl group, could suggest that the carbon chain is interrupted by an oxygen.

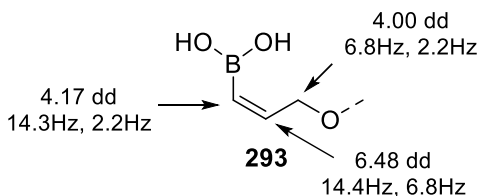
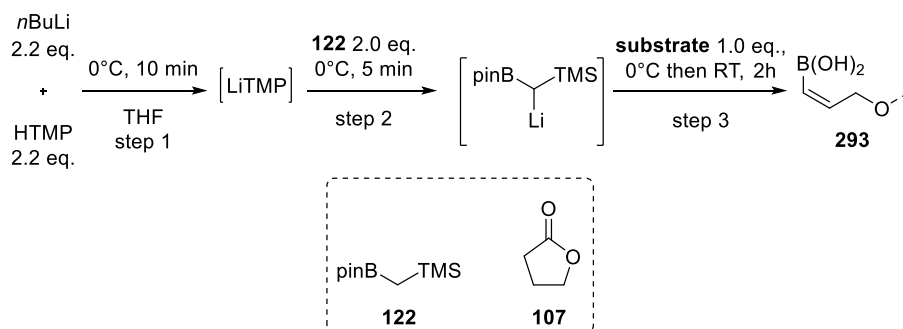


**Figure 34:**  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*) shifts of unknown product **293**.

The rest of the carbon skeleton of **293** could not be identified in this crude mixture but further experiments were carried out to gather more information on this borylated alkene product (**Table 24**).

**Table 24:** Formation of unidentified side product **293** using crown ether.



| Entry | Substrate      | Crown ether eq. | Addition | Yield <sup>a</sup> <b>293</b> (%) |
|-------|----------------|-----------------|----------|-----------------------------------|
| 1     | benzaldehyde   | 2.0             | Step 1   | 25 ( <b>222</b> )                 |
| 2     | <b>107</b>     | 2.0             | Step 1   | 28                                |
| 3     | <b>107</b>     | 2.0             | Step 2   | traces                            |
| 4     | <b>107</b>     | 2.0             | Step 3   | 0                                 |
| 5     | <b>107</b>     | 1.0             | Step 1   | 29                                |
| 6     | <b>107</b>     | 3.0             | Step 1   | 21                                |
| 7     | methylbenzoate | 2.0             | Step 1   | 17                                |
| 8     | none           | 2.0             | Step 1   | 7                                 |

*a. Yield determined on the crude mixture by  $^1\text{H}$  NMR using DMT as an internal standard.*

We first tested the influence of 12-crown-4 ether over our reference reaction using benzaldehyde (**Table 24**, **Entry 1**). The corresponding vinylboronate **222** was obtained, although in a lower yield than usual, and no unknown product **293** was detected. We then experimented with the order of addition (**Table 24**, **Entry 2-4**). It appeared

crucial to introduce the crown ether at the very beginning of the reaction to form the borylated alkene **293**.

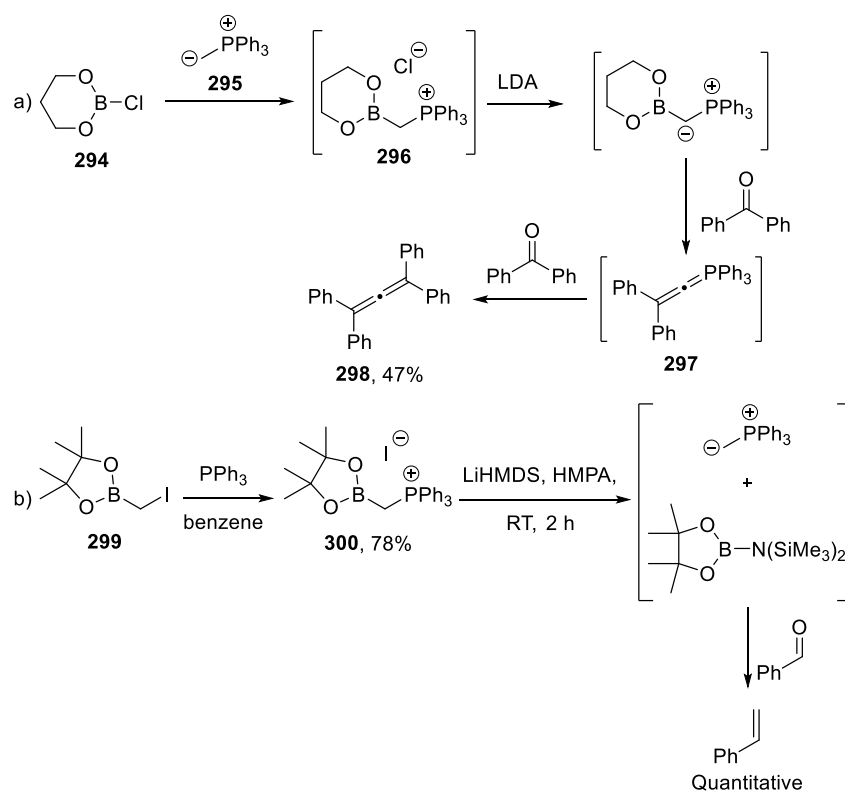
Next, we diminished the amount of crown ether to 1.0 equivalent and it did not alter the outcome of the reaction (**Table 24, Entry 5**). On the other hand, a slight decrease of the yield is observed when a three-equivalent excess of 12-crown-4 ether is used (**Table 24, Entry 6**).

With the idea of simplifying the structure of the formed vinylboronate to facilitate the analyses, the lactone substrate was replaced by methylbenzoate (**Table 24, Entry 7**). Curiously, the signals attributed to the same side-product **293** were observed. This thought-provoking result urged us to carry out the reaction in the absence of any substrate (**Table 24, Entry 8**). The formation of **293**, albeit in a low yield, demonstrate that the observed vinylboronate structure is formed from the crown ether's scaffold itself. However, the use of this complexing agent to capture lithium ions has been reported before, absent this reactivity.<sup>[188]</sup> Therefore we postulated that reagent **122** must take part in this borylation process. The yield variations when a carbonylated substrate was present point out that these substrates are not innocent bystanders during the formation of **293**.

As intriguing as this unexpected reactivity might be, **293** does not constitute a step towards the formation of borylated *exo*-glycols. In consequence, and pressed by the time, we concluded there our work on the Peterson reaction.

## 6. The Wittig reaction (with Julien Feytens, MSc)

As illustrated above, the Wittig reaction has been successfully applied to the synthesis of *exo*-glycols carrying electron withdrawing groups (see **Scheme 7**, page 7).<sup>[31]</sup> We envisioned to extend this method to the formation of borylated *exo*-glycols. However, suitable *gem*-borylphosphorylalkane reagents were only reported twice. In their 1983 publication, Matteson and Mujamdar generated the borylated phosphonium salt **296** from boronate chloride **294** and phosphonium ylide **295** (**Scheme 115**, a).<sup>[168]</sup> Upon deprotonation with LDA and reaction with benzophenone, the allene **298** is isolated in 47% yield. They indicated phosphonium ylide **297** as an intermediate, which would demonstrate that the boron-Wittig occurred before the Wittig reaction, but this compound was neither isolated nor discussed. Twenty years later, Srebnik *et al.* reported phosphonium salt **300**, synthesized in 78% yield following the substitution of  $\alpha$ -iodoboronate **299** (**Scheme 115**, b).<sup>[189]</sup> Instead of the deprotonation of the *gem*-borylphosphorylmethane, the addition of LiHMDS provoked the deborylation resulting from the complexation of the amide on the boron atom. This reactivity is surprising considering the bulkiness of the HMDS anion, but it was supported by the formation of styrene as a result of the olefination process with benzaldehyde.



**Scheme 115:** Olefination reactions with *gem*-borylphosphorylalkane by Matteson (a) and Srebnik (b).

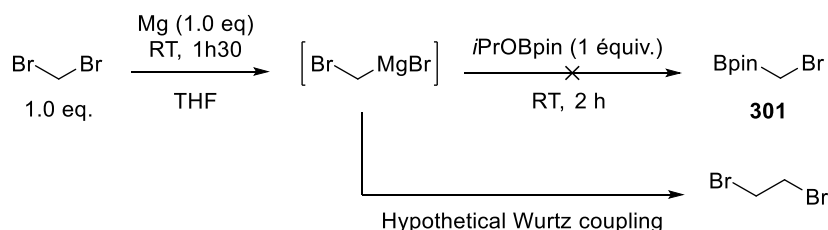
These reports illustrate the two strategies towards the synthesis of *gem*-borylphosphorylalkane that we will explore: the substitution of an  $\alpha$ -halogenoboronate, and the borylation of a phosphonium ylide.

### 6.1. Synthesis of $\alpha$ -halogenoboronates

To facilitate the subsequent substitution of the halogen with a triphenylphosphine, we focused on bromo and iodo derivatives. Inspired by our synthesis of *gem*-bisborylmethane **121** (see chapter 4.1, page 63), we endeavor to form  $\alpha$ -bromoboronate **301** via a metalation/borylation sequence starting from dibromomethane (**Scheme 116**). The total conversion of the starting bromide and the visually confirmed reaction of the magnesium indicated the *in situ* formation of the Grignard reagent. However, the desired borylated product **301** was not observed. It is



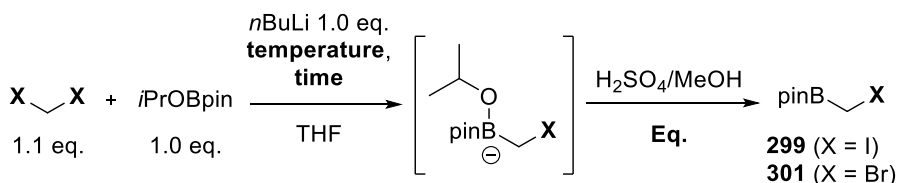
conceivable that the Grignard intermediate underwent a Wurtz homocoupling, even though the resulting dibromoethane was not detected by  $^1\text{H}$  NMR.



**Scheme 116:** Our attempt at synthesizing  $\alpha$ -bromoboronate **301** via a Grignard reaction.

We then decided to perform the reaction using an organolithium intermediate instead of the organomagnesium. The procedure reported by Renaud *et al.* served as a work base for these experiments.<sup>[190]</sup> Butyllithium was used for the metalation of diiodo- or dibromomethane in presence of the borylating reagent. An acidic work-up released the product in its desired trivalent form (**Table 25**).

**Table 25:** Synthesis of  $\alpha$ -halogenoboronate according to Renaud.



| Entry | X  | Temperature | Time | Eq. acid | Yield <sup>a</sup> (%) |
|-------|----|-------------|------|----------|------------------------|
| 1     | I  | RT          | 3h   | excess   | 1                      |
| 2     | Br | RT          | 3h   | 0.5      | traces                 |
| 3     | I  | RT          | 16h  | 0.5      | 40                     |
| 4     | I  | -78°C to RT | 16h  | 0.5      | 23                     |

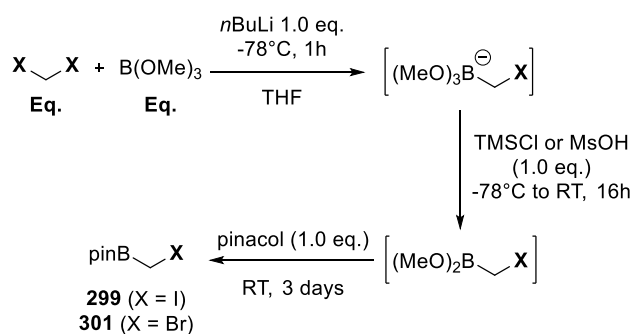
*a.* Yield determined on the crude mixture by  $^1\text{H}$  NMR using DMT as an internal standard.

According to the reaction conditions reported by Renaud *et al.*,<sup>[190]</sup> a three-hour procedure at room temperature was carried out, followed by an acidic quench with an excess of methanolic sulfuric acid (**Table 25, Entry 1**). The desired product was formed, although in negligible yield, but a significant amount of free pinacol is obtained. This observation pointed out to the excessive hydrolyzation of the boronate and prompted us to limit the use of the diacid to half an equivalent. Even with this precaution, the reaction using dibromomethane led to only traces of the desired product **301** (**Table 25, Entry 2**).

Extending the reaction time to sixteen hours increased the amount of **299** formed (**Table 25, Entry 3**). However, and considering the inevitable loss of product when a Bpin derivative is ran through silica, this yield was considered too low to justify a purification. A more cautious addition done at -78°C, followed by a slow warm up overnight led to an even lower NMR yield (**Table 25, Entry 4**).

In view of these results, we turned our attention to a related procedure from Matteson and Michnick,<sup>[180]</sup> exploited earlier in this thesis (see **Scheme 100**, page 135). TMSCl or MsOH was used to generate the trivalent methoxyboronate, which was then transesterified using pinacol (**Table 26**).

**Table 26:** Synthesis of  $\alpha$ -halogenoboronate according to Matteson.



| Entry | X  | CH <sub>2</sub> X <sub>2</sub> Eq. | B(OMe) <sub>3</sub> Eq. | TMSCl or MsOH | Yield <sup>a</sup> (%)    |
|-------|----|------------------------------------|-------------------------|---------------|---------------------------|
| 1     | I  | 1                                  | 1                       | TMSCl         | 49 (3 or 34) <sup>b</sup> |
| 2     | Br | 1                                  | 1                       | TMSCl         | 11                        |
| 3     | Br | 1                                  | 1                       | MsOH          | 59 (49) <sup>b</sup>      |
| 4     | Br | 1                                  | 1.5                     | MsOH          | 59 (48) <sup>b</sup>      |
| 5     | Br | 1.5 <sup>c</sup>                   | 1                       | MsOH          | 51                        |

*a.* Yield determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard; *b.* In brackets, yield in pure isolated compound; *c.* 1.5 eq. of *n*BuLi.

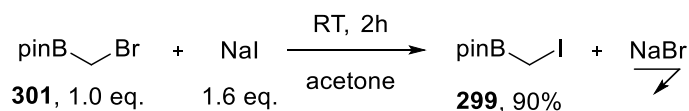
The reaction conducted following the reported reaction conditions led to a satisfying 49% as measured by <sup>1</sup>H NMR (**Table 26, Entry 1**). The diiodomethane was only partially converted, and a purification was necessary to remove the remnant. A flash chromatography was performed, only leading to a disappointing 3% yield of pure **299**. A distillation under reduced pressure proved to be more suited, but the collected product changed color. While the iodoboronate **299** is stable in its liquid state, its vapors are described to be light-sensitive.<sup>[190]</sup> Even when the distillation is conducted in the absence of light, the pure product is obtained in 34% yield at best.

In consequence, we turned our attention to the brominated alternative, which should better tolerate the purification by distillation.

Surprisingly, the conditions previously tested only led to an NMR yield of 11% (**Table 26, Entry 2**). Even more unexpected was the formation of the  $\alpha$ -chloroboronate (X = Cl). To get rid of any chloride anion in the reaction mixture, the TMSCl was replaced by MsOH (**Table 26, Entry 3**). The desired product **301** is obtained in a 59% NMR yield, and 49% after distillation under reduced pressure.

To further improve this result, variations of the reagent's proportions were tested. An excess of borylation agent didn't show any noticeable differences in the NMR or isolated yields (**Table 26, Entry 4**). A slight diminution of the NMR yield is observed when the quantity of dibromomethane is increased to 1.5 equivalents (**Table 26, Entry 5**).

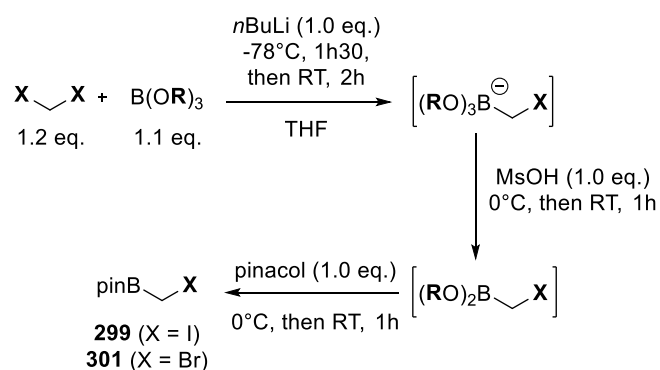
This reaction proved efficient for the synthesis of  $\alpha$ -bromoboronate **301**, but inadequate for the gram-scale synthesis and purification of the iodide counterpart **299**. The Finkelstein reaction provided a way around this issue. Using sodium iodide, the bromo derivative is converted into the  $\alpha$ -iodoboronate **299**, with the formation of sodium bromide, insoluble in acetone (**Scheme 117**). Although the displacement of a bromide by an iodide is disfavored, the precipitation of the side-product cleanly drives the reaction to completion.



**Scheme 117:** Conversion of the bromo derivative into its iodo counterpart.

The lengthy procedure described in **Table 26** slowed down our exploration of the borylating Wittig reaction. Therefore, we were interested in a similar protocol by Tanaka *et al.* that allowed us to conduct the whole reaction within one day (**Table 27**).<sup>[191]</sup>

**Table 27:** Synthesis of  $\alpha$ -halogenoboronate according to Tanaka.



| Entry | X  | R           | Yield <sup>a</sup> (%) |
|-------|----|-------------|------------------------|
| 1     | Br | Me          | traces                 |
| 2     | Br | <i>i</i> Pr | 56                     |
| 3     | I  | <i>i</i> Pr | 92                     |

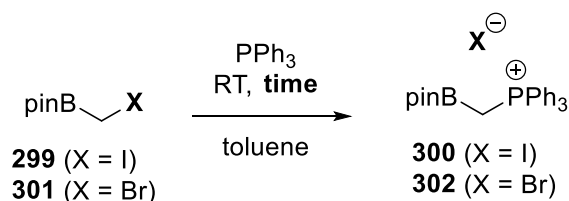
*a.* Yield determined on the crude mixture by  $^1\text{H}$  NMR using DMT as an internal standard.

Disappointingly, the reported reaction conditions only led to the desired product **301** in traces (**Table 27, Entry 1**). However, when the borylating reagent was swapped for the triisopropoxyborate, the brominated product was formed in yields on par with those observed previously (**Table 27, Entry 2**). Interestingly, the iodo derivative **299** was obtained in an excellent NMR yield with  $\text{B(O}i\text{Pr)}_3$ , and it was used without further purification (**Table 27, Entry 3**).

## 6.2. Synthesis of *gem*-borylphosphorylmethane

The next step towards our borylated Wittig reagent was the substitution of the halogen using triphenylphosphine. As it is a straightforward procedure, only the reaction duration was studied (**Table 28**). The choice of toluene as the reaction's solvent caused the precipitation of the phosphonium salt, which allow for the effortless purification of the product by filtration.

**Table 28:** Synthesis of *gem*-borylphosphorylmethane.



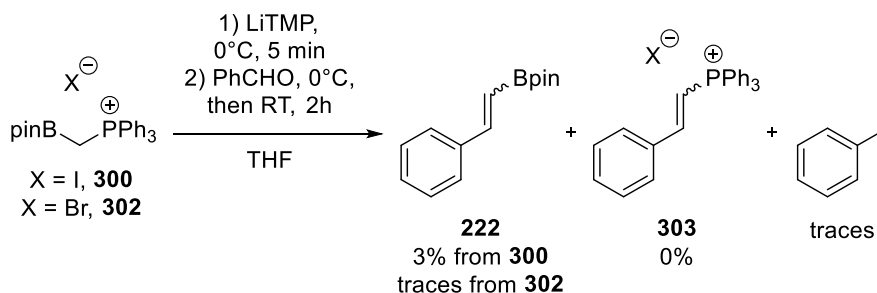
| Entry | X  | Time   | Yield (%) |
|-------|----|--------|-----------|
| 1     | I  | 30 min | 57        |
| 2     | I  | 2 h    | 68        |
| 3     | Br | 30 min | 40        |
| 4     | Br | 2 h    | 7         |

Our first attempt led to the iodide salt **300** in a decent 57% yield after a thirty minutes reaction (**Table 28, Entry 1**). The yield was further augmented to 68% when the reaction is prolonged to two hours (**Table 28, Entry 2**).

The reaction conducted on the  $\alpha$ -bromoboronate **301** behaved differently. While the desired bromide salt **302** was obtained in an average yield of 40% in thirty minutes (**Table 28, Entry 3**), a longer reaction time surprisingly led to a meager 7% yield (**Table 28, Entry 4**).

Nevertheless, with our phosphonium salts in hand, we started to investigate their reaction with benzaldehyde (**Scheme 118**). We used the reaction conditions optimized during our work on the Peterson olefination, but the phosphonium salts proved difficult to solubilize in THF. Even so, the borylated olefin **222** was observed in 3% NMR yield when the bromide salt **302** was used, and in traces when the reaction involved the iodide salt **300**. Only the *E* alkene was detected, but low signals corresponding to the *Z* isomer could simply be lost in the very chaotic  $^1\text{H}$  NMR spectra we recorded. For the same reason, the presence of the phosphorylated alkene **303** couldn't be confirmed. However, traces of styrene were indisputably

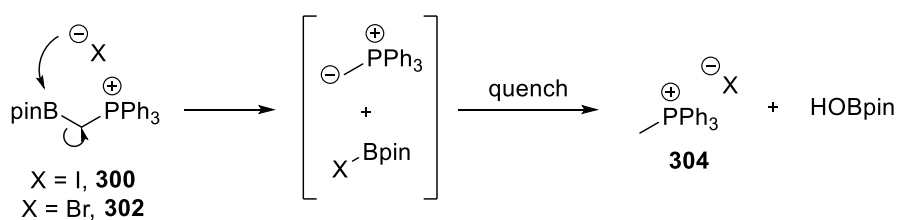
identified in both cases amidst the crude mixtures. This observation aligned with Srebnik's conclusion (see **Scheme 115, b**).



**Scheme 118:** Wittig olefination of benzaldehyde using borylated phosphonium salts **300** and **302**.

The formation of styrene as a result of the base-triggered deborylation of **300** or **302** seemed very unlikely, as the Bpin group was demonstrated on many occasions (including in this thesis) not to form an ate complex with TMP. The deborylation of **222** could also lead to the styrene side-product, but again, no such phenomenon was observed previously. Instead, we suspected that the phosphonium salt reagents were unstable. An additional  $^1\text{H}$  NMR spectrum was recorded using the initial sample of **300** still in deuterated acetone, three days after the first analysis. The protons borne by the central carbon shifted from 3.32 ppm to 3.23 ppm, and the Bpin signal, originally found at 1.04 ppm, was then observed at 1.24 ppm. To compare, a new sample was taken from the same batch of **300**. Both the phosphonium salt and the new specie were detected by  $^1\text{H}$  NMR analysis. Similar behavior was observed when **302** was analyzed again. Therefore, we concluded that the phosphonium halide salts degrade with time when they are isolated, and the phenomenon accelerates when the compounds are stored in solution.

We postulated that the formation of styrene must be the result of the olefination of benzaldehyde with methylphosphonium salt **304** (**Scheme 119**). This degradation product should arise from the deborylation of **300** or **302**, which is likely triggered by the complexation of the halide anion on the boron atom. The nature of **304**, confirmed by mass spectroscopy, disproves Srebnik theory on the formation of styrene during the olefination process.



**Scheme 119:** Deborylation of the phosphonium halide salts.

Aware of this stability issue, we prepared a fresh batch of **302** and directly involved it in an olefination reaction, but the composition of the crude mixture was the same as above. Therefore, we put our efforts into the synthesis of more stable borylated phosphonium salts, either by changing the boron group for a more robust one, or by replacing the counteranion by a less nucleophilic one.

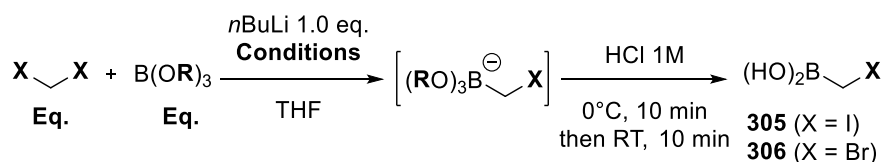
### 6.3. Variation of the borylated group

As described multiple times in this thesis, a modification of the boronic ester group will alter the electrophilicity of the boron atom. Therefore, BMIDA and  $\text{BF}_3\text{K}$  groups, for which the p orbital of the boron is partially or fully filled, would be less sensitive to the nucleophilic attack of the halide counterion.

The synthesis of these modified borylated phosphonium salt would first require the formation of an  $\alpha$ -halogenoboronic acid **305** ( $\text{X} = \text{I}$ ) or **306** ( $\text{X} = \text{Br}$ ), which will be further derived down the line. Our strategy is based on the synthesis of  $\alpha$ -halogenoboronates, though with an acidic hydrolysis instead of an esterification as the finishing step (**Table 29**).



**Table 29:** Synthesis of  $\alpha$ -halogenoboronic acid.



| Entry | X  | CH <sub>2</sub> X <sub>2</sub> Eq. | R           | B(OR) <sub>3</sub> Eq. | Conditions                 | Yield <sup>a</sup> (%) |
|-------|----|------------------------------------|-------------|------------------------|----------------------------|------------------------|
| 1     | Br | 1.2                                | <i>i</i> Pr | 1.1                    | -78°C 1.5h,<br>then RT, 2h | 29                     |
| 2     | Br | 1.0                                | <i>i</i> Pr | 1.5                    | -78°C to RT, 16h           | 49                     |
| 3     | Br | 1.0                                | Me          | 1.0                    | -78°C to RT, 16h           | 69 (35) <sup>b</sup>   |
| 4     | I  | 1.0                                | Me          | 1.0                    | -78°C to RT, 16h           | 45                     |

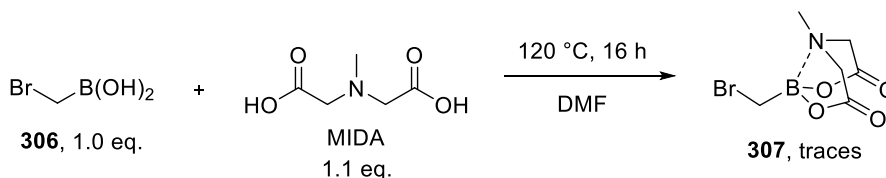
*a. Yield determined on the crude mixture by  $^1\text{H}$  NMR using DMT as an internal standard; b. In brackets, yield in pure isolated compound.*

Our first experiment used our reaction conditions inspired by Tanaka *et al.* (see **Table 27, Entry 2**). The desired product **306** is afforded in 29% yield, significantly lower than its pinacolboronate derivative **302** (**Table 29, Entry 1**). Like for the  $\alpha$ -silaneboronic acid **218**, product **305** and **306** were obtained in two forms: the monomeric one, and the boroxine trimeric one (see **Scheme 89**, page 115).

The reagents' proportion and the reaction duration were adjusted to better convert the starting dibromomethane, which resulted in a boost of the NMR yield (**Table 29, Entry 2**). Surprisingly, when the reaction was conducted using trimethoxyborate, deemed to be less reactive than its *isopropoxy* equivalent, it gave **306** in 69% NMR yield, reduced to 35% isolated yield upon washing the crude solid with DCM (**Table 29, Entry 3**). The same protocol applied to the iodo compound led to the formation of **305** in 45% NMR yield (**Table 29, Entry 4**). This dulled result can be explained by the lower conversion of the starting diiodomethane.

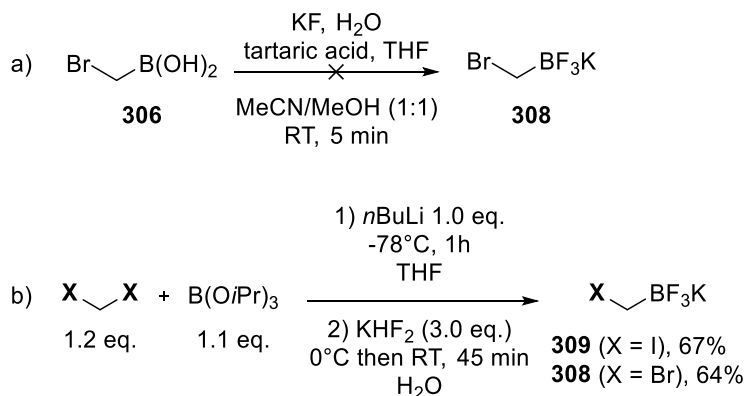
The  $\alpha$ -bromoboronic acid **306** was then esterified overnight using MIDA in refluxing DMF (**Scheme 120**). Disappointingly, only traces of the

desired BMIDA derivative **307** were obtained. Setting up water-trapping strategies such as the addition of molecular sieve to the reaction medium or installing a Dean-Stark apparatus (for which the solvent was modified to 2.5:1 toluene/DMF) did not improve this result.



**Scheme 120:** esterification of boronic acid **306**.

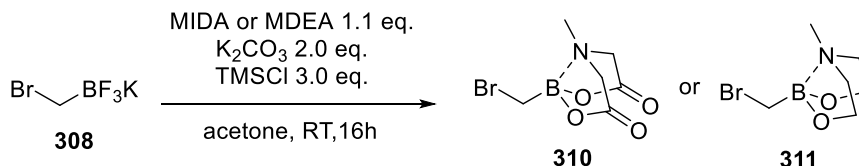
We then turned our attention to the trifluoroborate derivatives. The Lloyd-Jones protocol, that allowed us to synthesize the  $\text{BF}_3\text{K}$  reagent **166** for the boron-Wittig and **253** for the Peterson olefinations,<sup>[146]</sup> proved unsuccessful when applied to our halogeno compounds (**Scheme 121**, a). We tried another approach which consisted of the *in situ* fluorination following the borylation of halogenated compounds (**Scheme 121**, b). Both the iodo **309** and bromo **308** derivatives were obtained in good yields.



**Scheme 121:** Fluorination of  $\alpha$ -halogenoboron compounds.

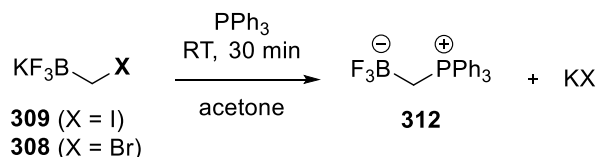
The defluorination strategy that successfully led to the Bcat Peterson reagent **255** was applied to the syntheses of the BMIDA and BMDEA  $\alpha$ -halogenoboronates **310** and **311** (**Scheme 122**). The reaction with MDEA led to the precipitation of a white solid, insoluble in any solvent, and thus not analyzable. For the reaction with MIDA, the solvent had to be

switched for DMF to dissolve this diacid. The desired product was formed within the complex crude mixture<sup>i</sup>, but only 10 mg were collected, starting from 200 mg of **308**.



**Scheme 122:** Synthesis of BMIDA and BMDEA derivatives via the defluorination method.

The synthesis of trifluoroborate phosphonium salts still required the substitution of the halogen with triphenylphosphine (**Scheme 123**). The reactions were done in acetone for solubility considerations. The brominated reagent **308** showed no signs of conversion after thirty minutes at room temperature. We continued this work with the iodo derivative, bearing a better leaving group, and we carried out the reaction at reflux during three hours. An interesting doublet was observed in the <sup>1</sup>H NMR spectrum of the crude mixture, which could be the result of a J<sup>2</sup><sub>H-P</sub> coupling. However, further analyses could not be done at that time.

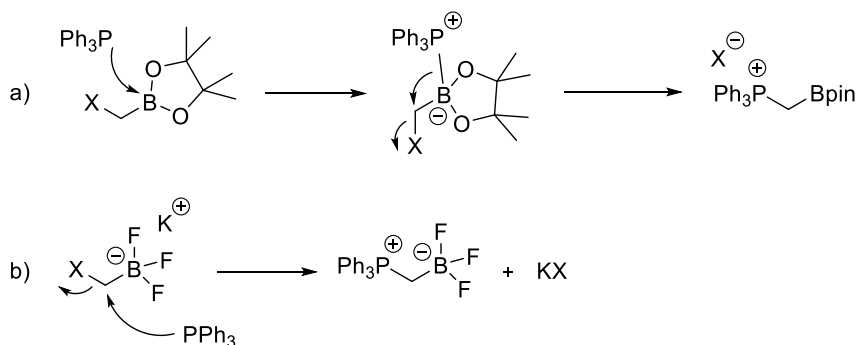


**Scheme 123:** Substitution on trifluoroboronates **308** and **309**.

The difficult substitution of the trifluoroborate compounds, compared to their Bpin equivalents, can be rationalized due to the tetravalent form of the boron. In the Bpin derivatives, substitution using amines was shown to proceed with the assistance of the boron atom.<sup>[192]</sup> This mechanism could be extended to the addition of the phosphorus on the boron, before a 1,2-migration provokes the displacement of the

<sup>i</sup> <sup>1</sup>H NMR (600 MHz, Chloroform-*d*) δ 3.82 (d, *J* = 16.2 Hz, 2H), 3.68 (d, *J* = 16.2 Hz, 2H), 2.91 (s, 3H), 0.16 (s, 2H).

halogen (**Scheme 124**, a). This two-steps mechanism cannot occur on the tetravalent trifluoroborate, for which a regular  $S_N2$  is considered (**Scheme 124**, b).



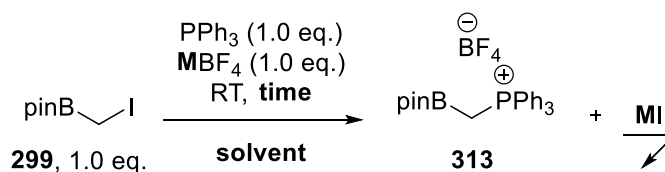
**Scheme 124:** Substitution mechanism on trivalent (a) and tetravalent (b) α-halogenoboronates.

In our previous chapter on the Peterson olefination, we demonstrated that borylated moiety more stable than Bpin tended to render the molecules less soluble and their deprotonation more challenging. The replacement of the silane moiety by a phosphonium group should lower the pKa of the adjacent protons, solving the deprotonation issue. The lack of solubility, however, should still be observed, or even worsened, in the case of the phosphonium salts. Therefore, and considering the absence of promising results regarding the variation of the borylated group, we moved to our next strategy, the modification of the counteranion.

### 6.3. Modification of the counteranion

Considering that the borylated salts underwent deborylation due to the postulated action of the halide, we were interested in the synthesis of salts containing less nucleophilic counteranions, such as **313**. Accordingly, we attempted to capture the iodide, released during the substitution by PPh<sub>3</sub>, by using sodium or silver tetrafluoroborate (**Table 30**). Iodide should precipitate out of the solution in the form of NaI or AgI.

**Table 30:** Phosphonium salt anion exchange attempts.



| Entry | M  | Solvent | Time | Result                             |
|-------|----|---------|------|------------------------------------|
| 1     | Na | DMF     | 16 h | Deborylated salt <b>304</b>        |
| 2     | Na | toluene | 2 h  | Unstable borylated salt <b>300</b> |
| 3     | Ag | toluene | 2 h  | Starting materials                 |

We selected DMF for our first experiment as this solvent is able to dissolve NaBF<sub>4</sub>, but will cause the NaI side-product to precipitate (**Table 30, Entry 1**). However, no precipitate was observed after two hours of reaction. We decided to keep the reaction running overnight, but only the deborylated salt **304** was observed as a result.

The next reaction was carried out in toluene, in which the formed NaI should precipitate (**Table 30, Entry 2**). However, the sodium tetrafluoroborate was also found to be barely soluble in this solvent. After two hours of reaction, a borylated phosphonium salt was isolated, but no signals appeared on the <sup>11</sup>B NMR spectrum. Furthermore, the analyses were repeated the next day, with only the deborylated salt **304** being detected. In consequence, the initially formed salt is postulated to be the borylated phosphonium iodide **300**.

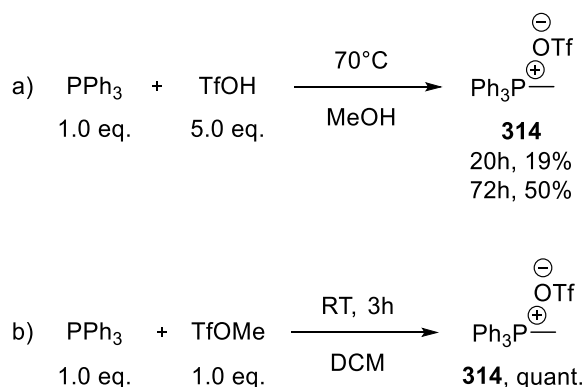
The metallic salt was changed to silver tetrafluoroborate, which is soluble in toluene and should facilitate the anion exchange (**Table 30, Entry 3**). Surprisingly, neither the deborylated salt **304** nor the iodide salt **300** were obtained. The starting materials were recovered, showing signs of degradation.

Facing these difficulties in replacing the iodide counteranion, we decided to explore another synthetic route in which halides wouldn't be involved at all. Instead of the phosphorylation of a borylated compound, we

investigated the borylation of a phosphonium salt, as reported by Matteson (see **Scheme 115**, a).<sup>[168]</sup> A suitable precursor, the phosphonium triflate **314**, has been previously described, although not as an isolated compound but only as an *in situ* generated intermediate.<sup>[193]</sup>

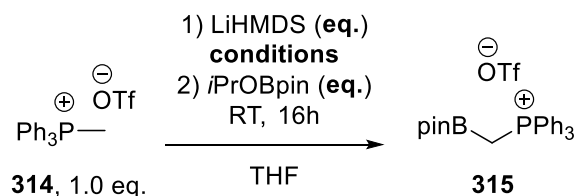
We conducted an adapted procedure to obtain the desired salt **314** (**Scheme 125**, a). After twenty hours of reaction, the phosphonium triflate was obtained in only 19% yield. A three-days reaction afforded the product with an improved yield of 50%, still an underwhelming result. The treatment of the crude also suffered from low reproducibility. Upon evaporation of the methanol, DCM was added to the crude, which led to a biphasic mixture. The top phase consisted of the desired product in solution in DCM (which is precipitated using Et<sub>2</sub>O), while the bottom phase was the excess triflic acid (TfOH).

A much simpler protocol has been reported by Tolstikova *et al.* (**Scheme 125**, b).<sup>[194]</sup> We were able to replicate their work which gave **314** in a quantitative yield.



**Scheme 125:** synthesis of phosphonium triflate **314**.

We then studied the borylation of this phosphonium triflate **314** (**Table 31**). The salt must be deprotonated using a strong base, before the ylide thus formed can add to a borylating reagent. For this purpose, we selected *i*PrOBpin which was the most successful in our previous chapters.

**Table 31:** Synthesis of phosphonium triflate **315**.

| Entry          | Eq. base | Conditions                 | Eq. <i>i</i> PrOBpin | Ratio 314/postulated 315 |
|----------------|----------|----------------------------|----------------------|--------------------------|
| 1 <sup>a</sup> | 1.1      | -78°C, then<br>0°C, 30 min | 1.0                  | 0.85 : 1                 |
| 2              | 1.1      | -78°C, then<br>0°C, 2 h    | 1.0                  | 0.45 : 1                 |
| 3              | 2.2      | 0°C, 2 h                   | 1.1                  | 0.4 : 1                  |
| 4              | 1.1      | 0°C, 2 h                   | 2.2                  | 0.5 : 1                  |
| 5 <sup>b</sup> | 1.1      | 0°C, 2 h                   | 1.0                  | 0 : 1                    |

*a.* reaction carried out during 2h; *b.* reaction carried out using NaH as a base.

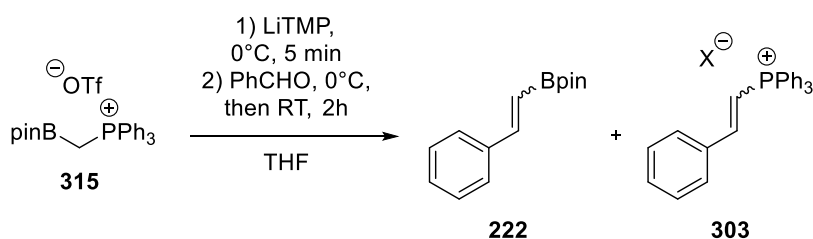
In our first attempt, LiHMDS was used as the base and was added at -78°C, and the deprotection was carried on during thirty minutes using an ice bath (**Table 31, Entry 1**). The borylation then proceeded for two hours, after what a new product was formed. This compound, represented by a doublet at 2.02 ppm and a singlet typical of a Bpin moiety, was postulated to be **315**. The conversion was however low, so in our second attempt the borylation was performed overnight (**Table 31, Entry 2**). This led to an improvement of the crude mixture's proportion, but the transformation of **314** remained incomplete.

We doubled the amount of base, a modification that barely had an impact on the conversion, but complexified the crude's NMR spectrum (**Table 31, Entry 3**). A similar result was obtained when the quantity of the borylated reagent was doubled instead (**Table 31, Entry 4**). It is noteworthy

that the crude was analyzed once more after a day, and no alteration of the NMR spectrum was observed.

In order to drive the reaction to completion, we tested the non-hindered base sodium hydride (**Table 31, Entry 5**). We were satisfied to see that the 2.02 ppm signal of the postulated **315** was formed, and no traces of the starting **314** were detected. However, no Bpin moiety was detected, which cast doubt on the nature of the newly formed product.

The best crude mixture obtained so far, under the reaction conditions reported in **Entry 2**, was involved in an olefination procedure with benzaldehyde (**Scheme 126**). Should the borylated olefin be observed, it would have supported the presence of **315** within the reaction medium. Unfortunately, neither **222** nor **303** were observed, which could indicate that **315** was not synthesized at all. Interestingly, the styrene that would result from the olefination using the unconverted **314** was not found. This could indicate that our olefination conditions were not suited to Wittig reactions.



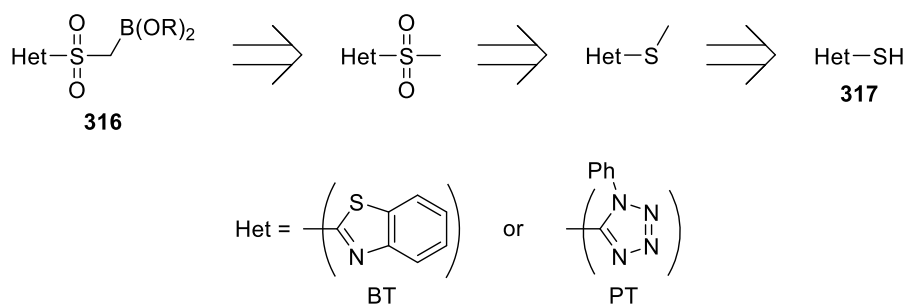
**Scheme 126:** olefination attempt using postulated phosphonium salt **313**.

To conclude this chapter, our first targets, the borylated  $\alpha$ -halogenophosphonium salts allowed us to perform the first vinylboronate *via* a Wittig reaction, but they also proved unstable in time. Considering that the counteranion modification strategy was unsuccessful, and that only insoluble products were obtained when we varied the borylated group, we moved on to our last olefination method.



## 7. The modified Julia reaction (with Julien Feytens, MSc)

Among the efficient method for the synthesis of *exo*-glycals, the modified Julia reaction is probably the most successful one (see chapter 1.1.2.1., page 6). However, the formation of vinyl boronates *via* a Julia olefination has never been reported. Such a transformation would require an  $\alpha$ -borylsulfone **316** which, to the best of our knowledge, is still unheard of. To afford this sort of species, one can visualize three modifications of a starting heteroaromatic thiol **317**: the addition of a carbon, the oxidation of the sulfur atom, and the borylation itself (**Scheme 127**). We could foresee that these individual steps could be combined, and their sequence could be adjusted. We decided to work on the widely spread benzothiazole (BT) and phenyltetrazole (PT) heteroaromatic groups.



**Scheme 127:** Synthetic steps necessary for the formation of  $\alpha$ -borylsulfone **316** from thioether **317**.

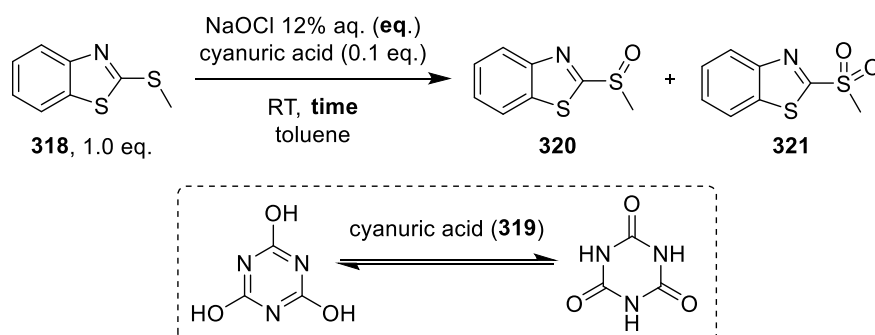
### 7.1. Synthesis of $\alpha$ -borylsulfones by borylation of sulfones

Considering that borylated group can be sensitive to oxidation conditions, we focused first on the transformation of the thiol to a sulfone prior to the borylation step. Furthermore, as the sulfur methylation of a sulfone is unlikely, the thiol must be converted to a methylthioether which will undergo oxidation. The methylated sulfone thus obtained would then be functionalized by a boryl group.

Regarding the benzothiazole heteroaromatic group, the thioether **318** was commercially available. For its oxidation, we used a biphasic

bleach-based reaction, with cyanuric acid **319** acting as a non-classical phase-transfer catalyst (**Table 32**).<sup>[195]</sup> A chloration step in the aqueous phase forms a trichlorocyanuric acid, which returns in the organic phase to perform the oxidation of the thioether **318** into the sulfoxide **320**, this latter entering the catalytic cycle once more to give the sulfone **321**.

**Table 32:** Oxidation thioether **318**.



| Entry | Eq. NaClO | Time (h) | Ratio <b>320</b> / <b>321</b> <sup>a</sup> | Yield <sup>a</sup> |
|-------|-----------|----------|--------------------------------------------|--------------------|
| 1     | 3.3       | 3        | 94 : 6                                     | 6                  |
| 2     | 5.0       | 3        | 93 : 7                                     | 7                  |
| 3     | 3.3       | 5        | 3 : 97                                     | 94                 |
| 4     | 3.3       | 16       | 0 : 100                                    | 93                 |

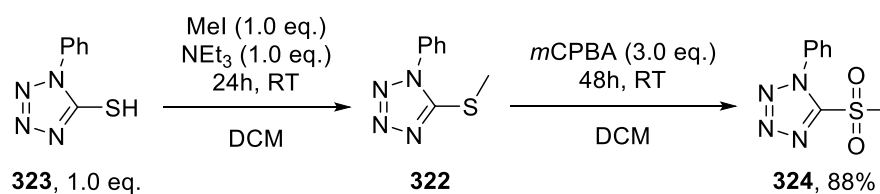
*a. Determined on the crude mixture by <sup>1</sup>H NMR using DMT as an internal standard*

Our first experiment led to the formation of sulfoxide **320** as the major product (**Table 32, Entry 1**). Although the desired product **321** is observed, the oxidation had to be pushed further. The equivalents of sodium hypochlorite were increased, without any significant improvements (**Table 32, Entry 2**). Instead, the reaction time was extended from three to five hours, which satisfyingly led to an inversion of the sulfoxide/sulfone proportions (**Table 32, Entry 3**).

The reaction was lengthened to an overnight procedure to fully oxidize the intermediate sulfoxide (**Table 32, Entry 4**). After a simple basic

work up, the desired product **321** was obtained with an excellent yield, on a multi-gram scale.

For the other heteroaromatic group, the phenyltetrazole-based thioether **322** was not available and had to be prepared by methylating the corresponding thiol **323**. This reaction was combined with an oxidation step to give the desired sulfone **324** in 88% over the sequence (**Scheme 128**).



**Scheme 128:** The two-step synthesis of sulfone **324**.

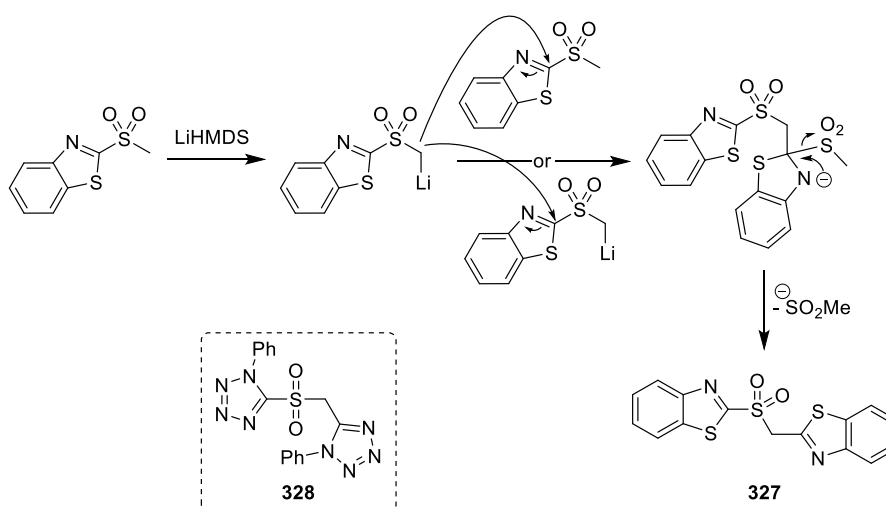
Before any modified Julia olefination attempts, these two heteroaromatic methylsulfones **321** and **324** would first need to be borylated. While this operation has never been reported, the functionalization of such sulfones is quite common. These procedures begin with a deprotonation, for which the use of 2.2 equivalents of LiHMDS is often reported (**Table 33**).<sup>[196]</sup>

**Table 33:** Investigation of the borylation of sulfones **321** and **324**.

| $  \begin{array}{c}  \text{Het}-\text{S}(=\text{O})_2- \\  \xrightarrow[\text{conditions 2}]{\begin{array}{l} \text{1) base (2.2 eq.)} \\ -78^\circ\text{C, 5 min} \\ \text{2) BR}_3 \text{ (1.1 eq.)} \end{array}} \\  \text{321, Het = BT} \\  \text{324, Het = PT}  \end{array}  \longrightarrow  \begin{array}{c}  \text{Het}-\text{S}(=\text{O})_2-\text{Bpin} \\  \text{325, Het = BT} \\  \text{326, Het = PT}  \end{array}  +  \begin{array}{c}  \text{Het}-\text{S}(=\text{O})-\text{CH}_2\text{Het} \\  \text{327, Het = BT} \\  \text{328, Het = PT}  \end{array}  $ |     |                     |                                            |                                |                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---------------------|--------------------------------------------|--------------------------------|---------------------------|
| Entry                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Het | Base                | BR <sub>3</sub>                            | Conditions 2                   | Result                    |
| 1 <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | BT  | LiHMDS              | <i>i</i> PrOBpin                           | -78°C, 30 min, then 0°C, 1.5 h | <b>327</b>                |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiHMDS              | <i>i</i> PrOBpin                           | 0°C to RT, 16 h                | <b>327</b>                |
| 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiHMDS <sup>b</sup> | <i>i</i> PrOBpin                           | -78°C to RT, 16 h              | <b>327</b> and <b>321</b> |
| 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiTMP <sup>b</sup>  | <i>i</i> PrOBpin                           | -78°C, 30 min, then 0°C, 1.5 h | <b>321</b>                |
| 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiTMP               | <i>i</i> PrOBpin                           | -78°C, 30 min, then 0°C, 1.5 h | <b>327</b> and <b>321</b> |
| 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiTMP               | <i>i</i> PrOBpin                           | -78°C to RT, 16 h              | <b>327</b>                |
| 7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | BT  | LiHMDS              | B <sub>2</sub> pin <sub>2</sub>            | -78°C, 30 min, then 0°C, 1.5 h | <b>327</b>                |
| 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PT  | LiHMDS              | <i>i</i> PrOBpin                           | -78°C, then 0°C, 1.5 h         | <b>328</b> and <b>324</b> |
| 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PT  | LiHMDS              | B <sub>2</sub> pin <sub>2</sub>            | -78°C, then 0°C, 1.5 h         | <b>324</b>                |
| 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | PT  | LiHMDS              | B( <i>Oi</i> Pr) <sub>3</sub> <sup>c</sup> | -78°C, then 0°C, 1.5 h         | <b>324</b>                |
| 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | PT  | LiHMDS              | BBr <sub>3</sub> <sup>c</sup>              | -78°C, then 0°C, 1.5 h         | <b>324</b>                |

*a.* Deprotonation step during 15 minutes; *b.* 1.1 eq. of base were used; *c.* The corresponding product would be the boronic acid.

Our first experiment showed the complete conversion of the starting methylsulfone into a new compound (**Table 33, Entry 1**). Once purified by flash chromatography, it was identified as product **327**, the result of the autocondensation of the sulfone. Such side-reactivity has already been reported, and would lead to the structure **328** when phenyltetrazole is used as the heteroaromatic group (**Scheme 129**).<sup>[197]</sup>



**Scheme 129:** autocondensation leading to **327** and its PT counterpart **328**.

Our subsequent efforts aimed at preventing this side-reaction. The deprotonation duration was reduced in order to involve the borylated reagent in the reaction as soon as possible. The temperature of the borylation step was also raised to favor the process (**Table 33, Entry 2**). Despite these precautions, the autocondensation product **327** was still obtained, with no trace of the desired product. Lowering the equivalent of base to 1.1 led to an incomplete conversion of the starting sulfone, but the formation of **327** was still preferred over the borylation (**Table 33, Entry 3**).

We feared that the HMDS produced during the deprotonation was poisoning the borylated reagent. Consequently, we turned to LiTMP, which has proved in our previous work to be too bulky to form an ate complex with the boron moiety. The use of 1.1 equivalent of that base did not allow for any conversion of the starting sulfone (**Table 33, Entry 4**). The amount of LiTMP was raised to 2.2 equivalents, which led to the partial transformation of the starting material into the autocondensation product,

while no borylated **325** was detected (**Table 33, Entry 5**). When the reaction is slowly warmed up overnight, the conversion of the sulfone was driven to completion, but **327** is the only product observed (**Table 33, Entry 6**).

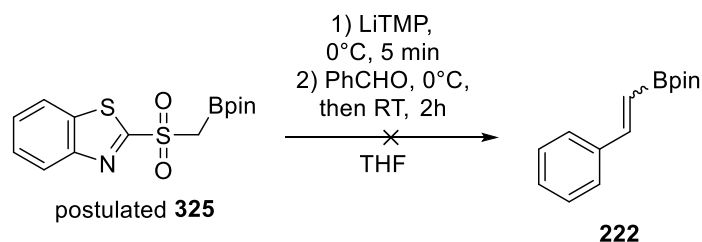
The formation of this autocondensation product indicated that the anion as a tendency to add onto another sulfone present in the reaction medium rather than the borylated reagent. We envisioned that different borylated reagents could prove beneficial to the reaction. Unfortunately, the use of bispinacolatodiboron B<sub>2</sub>pin<sub>2</sub> gave the same product **327** (**Table 33, Entry 7**).

We switched the starting material to the PT sulfone **324** in hope that this substrate would be less prone to autocondensate. Sadly, the LiHMDS deprotonation followed by the reaction with *i*PrOBpin led to a mixture of starting **324** and autocondensation product **328** (**Table 33, Entry 8**). Using alternative borylated reagent only resulted in the recovery of the starting sulfone **324** (**Table 33, Entry 9-11**). By comparing **Entry 8** with **Entry 1**, or **Entry 9** with **Entry 7**, it appeared the PT heteroaromatic group was indeed less inclined to autocondensate.

In an attempt to favor the borylation, we carried out an experiment in which the borylated reagent was mixed with the sulfone **321** before the LiHMDS was added dropwise. Although the autocondensation product was once more the major constituent of the crude mixture, a new set of signals were detected by <sup>1</sup>H NMR analysis.<sup>i</sup> These signals could match the ones we would expect for the borylated sulfone **325**, but this result couldn't be confirmed. Instead, we carried out an olefination reaction with this crude mixture, hoping to observed vinylboronate **222** (**Scheme 130**).

---

<sup>i</sup> <sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 7.35-7.32 (m, 2H), 7.17-7.06 (m, 2H), 4.96 (s, 2H), 1.17 (s, 12H).



**Scheme 130:** olefination attempt using postulated sulfone **325**.

Since the borylated product **222** did not form, the synthesis of **325** couldn't be confirmed. However, this disappointing result could also indicate that our olefination conditions, optimized for the Peterson reaction, were not suited for the modified Julia olefination. Indeed, an experiment was conducted under these conditions, using the methylsulfone **321**, with only traces of styrene being obtained.

It would appear that the autocondensation was always prevalent during the borylation of sulfones. Should the borylation be performed on the thioether **318** or **322** instead, we foresaw that the attack of one deprotonated sulfide onto another would be less favorable, and potentially reversible. However, considering that the deprotonation of a thioether might not be a straightforward process, we decided to test other synthesis routes first.

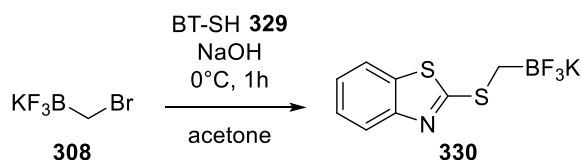
## 7.2. Synthesis of $\alpha$ -borylsulfones by substitution of an $\alpha$ -halogenoboronate

Similarly to our work on the synthesis of a borylated Wittig reagent, we envisioned that borylated thioether could be obtained *via* the nucleophilic substitution of an  $\alpha$ -halogenoboronate by a thiol. As a result, the subsequent oxidation to the corresponding sulfone would have to be performed in presence of a sensible borylated group. However, it is conceivable that the oxidation thioether can be achieved under conditions mild enough to leave the borylated group unaffected.

Additionally, our work on the Wittig reagent put to light the deborylation underwent by the compounds **300** and **302** when the Bpin group was in contact with a halide counteranion. This prompted us to use

more stable boron groups such as trifluoroborate  $\text{BF}_3\text{K}$  (see chapter 6.3, page 182). Coincidentally, such borylated group would also be less susceptible to oxidation conditions.

The bromide **308** was reacted with benzothiazole-2-thiol **329** at  $0^\circ\text{C}$  for an hour (**Scheme 131**). The  $^1\text{H}$  NMR analysis of the crude mixture showed a singlet at 0.13 ppm which could correspond to the hydrogen adjacent to the trifluoroborate in the desired product **330**. However, the signals of two additional benzothiazole compounds can be seen also. Compared to these side-products, the compound **330** should display a different solubility owing to its trifluoroborate moiety. Unfortunately, our attempt to take advantage of that hypothesis and to precipitate the desired borylated thioether was ineffective. Due to time limitation, no further attempt at synthesizing **330** were made.



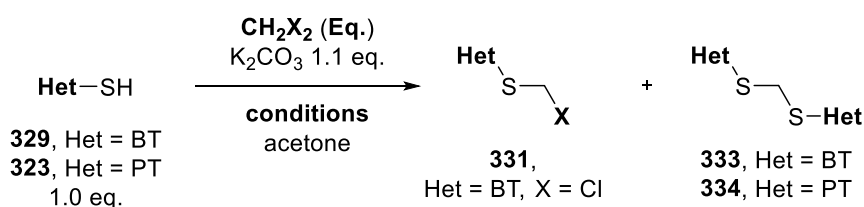
**Scheme 131:** Substitution on trifluoroboronates **308** using BT-thiol **329**.

### 7.3 Synthesis of $\alpha$ -borylsulfones by borylation of an $\alpha$ -halogenothioether

Another pathway towards borylated thioether was explored. It involved the metalation/borylation of an  $\alpha$ -halogenothioether, which was obtained through a substitution reaction on dihalogenomethane (**Table 34**).



**Table 34:** Synthesis of  $\alpha$ -halogenothioethers *via* a substitution strategy.

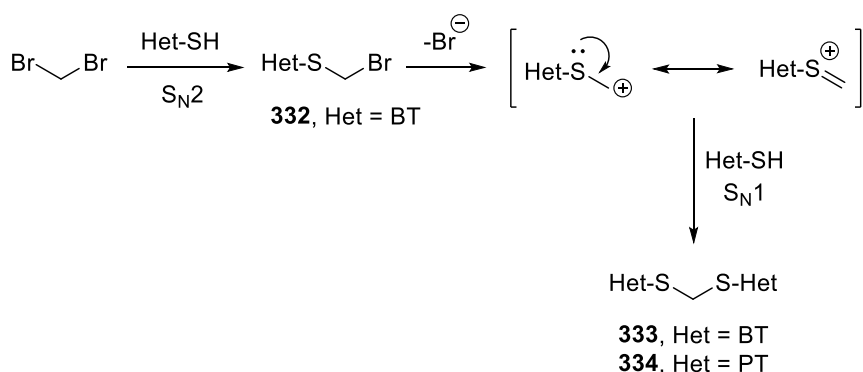


| Entry | Het | CH <sub>2</sub> X <sub>2</sub>  | CH <sub>2</sub> X <sub>2</sub> Eq. | Conditions  | Result                |
|-------|-----|---------------------------------|------------------------------------|-------------|-----------------------|
| 1     | BT  | CH <sub>2</sub> Br <sub>2</sub> | 1.0                                | Reflux, 2 h | <b>333</b>            |
| 2     | BT  | CH <sub>2</sub> Br <sub>2</sub> | 1.0                                | 0°C, 1 h    | <b>333</b>            |
| 3     | PT  | CH <sub>2</sub> Br <sub>2</sub> | 1.0                                | 0°C, 2 h    | <b>334</b>            |
| 4     | PT  | CH <sub>2</sub> Br <sub>2</sub> | 5.0                                | 0°C, 1 h    | <b>334</b>            |
| 5     | BT  | CH <sub>2</sub> ICl             | 1.0                                | 0°C, 1 h    | <b>331/333</b> = 10:1 |
| 6     | BT  | CH <sub>2</sub> ICl             | 1.0                                | 0°C, 30 min | <b>331/333</b> = 15:1 |

With a single equivalent of thiol **329**, we were expecting to obtain the mono substitution product. Indeed, the variation of steric effects, introduced by the first substitution leading to  $\alpha$ -bromothioether **332**, shouldn't favor the disubstitution process. At worst, we anticipated a mixture of mono- and disubstituted product. However, our first conditions (**Table 34, Entry 1**) afforded only the disubstituted **333**. Understandably, as two equivalents of thiol were consumed by one equivalent of dibromomethane, only half of this reagent was converted.

As our reaction conditions were, admittedly, unnecessarily harsh, we performed the reaction again at a lower temperature (**Table 34, Entry 2**). Once more, the dibromomethane underwent the double thiol-substitution. We turned our attention to the phenyltetrazole group, as the steric hinderance introduced by the side phenyl group should slow down the second substitution (**Table 34, Entry 3**). This strategy proved insufficient as the doubly substituted product **334** was obtained. An increased of the dibromomethane equivalent, which should statistically favor the monosubstituted product, failed also (**Table 34, Entry 4**).

These last results convinced us that the substitution mechanism was more complex than anticipated (**Scheme 132**). In contrast with the first substitution step, which proceeds in a  $S_N2$  manner, the release of a bromide from intermediate **332** would be encouraged by the existence of a stabilizing mesomeric effect. The second substitution is therefore postulated to occur *via* a  $S_N1$  reaction.



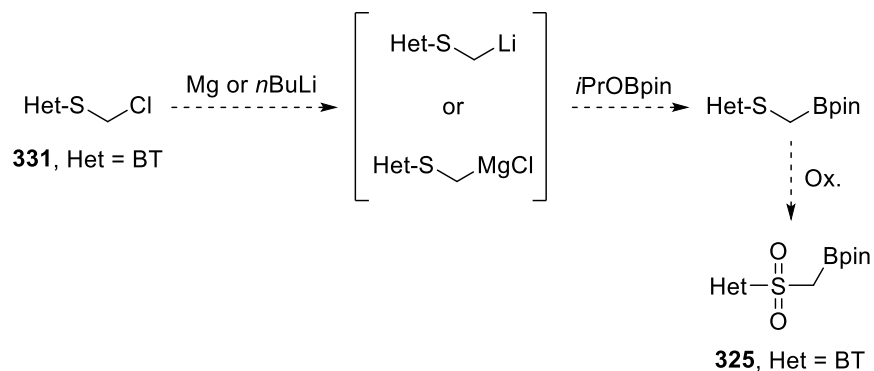
**Scheme 132:** the double substitution of dibromomethane by a thiol.

As it would appear that the dibromomethane could not be selectively monosubstituted, we instead turned our attention to another substrate more suited to our need, the chloriodomethane. The iodide was to be selectively substituted in an initial  $S_N2$  step, leading to an  $\alpha$ -bromothioether. Despite the donating mesomeric effect of the sulfur, the chloride is a weak leaving group, which should prevent to subsequent  $S_N1$  to happen.

This approach allowed for the synthesis of the desired  $\alpha$ -chlorothioether **331** (**Table 34**, **Entry 5**). The crude mixture was composed only of the desired product and the disubstituted **333**, in a very favorable ratio. A reduced reaction time further improved the selectivity toward the monosubstituted product (**Table 34**, **Entry 6**).

Shorter reaction duration might allow for the selective synthesis of **331**. This product would then have to undergo a metal/chloride exchange via a Grignard or a lithiation reaction in order to be borylated (**Scheme 133**). The corresponding sulfone would then be the result of an oxidation step, which might require the modification of the boron group to a more

resilient one. Unfortunately, this work couldn't be pursued further due to a lack of time.



**Scheme 133:** Strategy toward borylated sulfone **325** from  $\alpha$ -chlorothioether **331**.

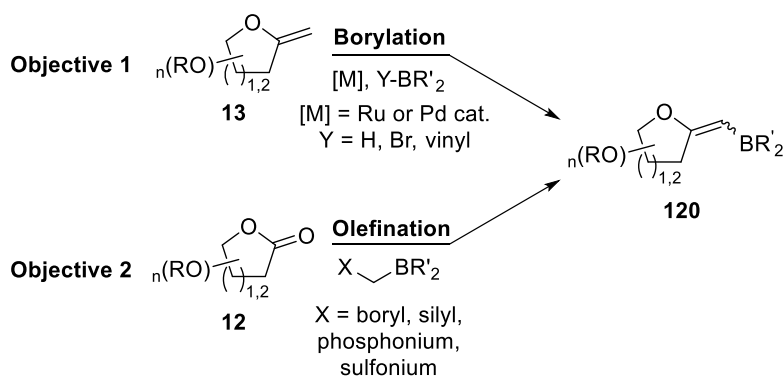
Our first envisioned synthetic route faced a manifest side-reaction issue with the autocondensation of the sulfone. This forced us to adapt our reaction sequence to avoid having to perform the challenging borylation of the sulfone. While the new strategy has to be further explored, results were encouraging.



## 8. Conclusions and perspectives

Our project aimed at the synthesis of the first borylated *exo*-glycols. Although this outcome remains beyond our reach, advances were made during our exploration of the olefination strategies involved.

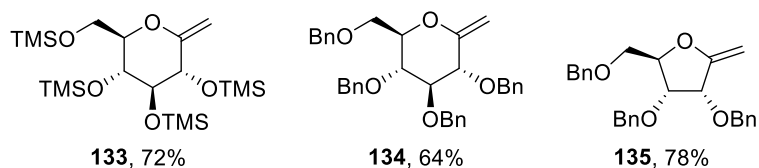
We envisioned two main routes towards borylated *exo*-glycols: the functionalization of a pre-formed *exo*-cyclic carbon-carbon double bond, and the borylating olefination of sugar lactones (**Scheme 48**). This second strategy can be further divided between the boron-Wittig and the Peterson reactions, that already proved to be efficient in borylating olefinations, and the Wittig and modified Julia reactions, for which the required borylated reagent remained to be synthesized.



**Scheme 48:** General objectives of this work.

### 8.1. Borylation of methylene *exo*-glycols

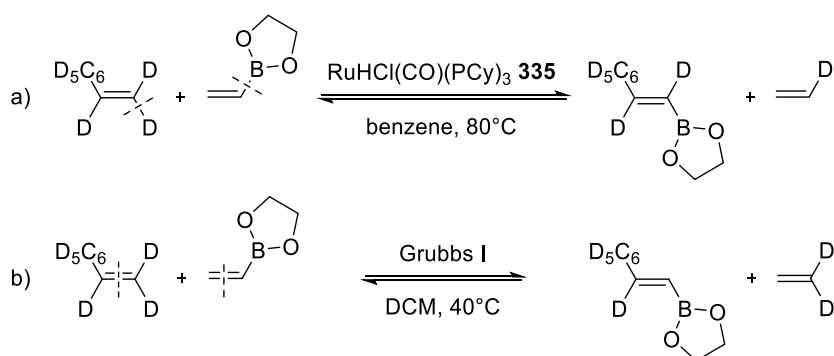
These methods suffer from the usage of complex substrates exhibiting a low stability. Three such methylene *exo*-glycols were synthesized *via* a Petasis olefination, covering different ring sizes and protecting groups (**Scheme 50**). While many methods were reported for the borylation of alkenes, very few were successfully applied to enol ethers, which illustrated the challenge that represents the conversion of our substrates.



**Scheme 50:** Synthesis of methylene *exo*-glycals.

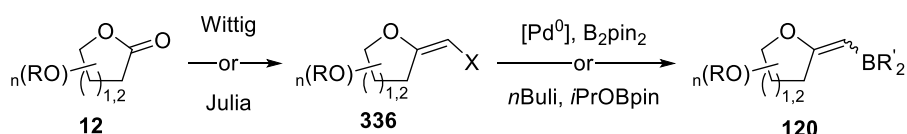
Recent reports on the Heck reaction showed the possibility to carry out the reaction on *exo*-glycal substrates (Bolshan) or using borylated reagent (Watson *et al.*). We endeavored to combine their work into a procedure that would accommodate both of these features: a boryl-Heck reaction on a methylene *exo*-glycal. Sadly, none of our experiments led to promising results, with the degradation of the substrates being the main observation.

The olefin metathesis reaction has been reported on enol ether substrates. Therefore, this approach was tested using methylene *exo*-glycal substrates. Both Grubbs I and Grubbs II catalysts failed to yield the desired product, with the homocoupling of the vinylboronate reagent being the only product formed while our substrates remained inert. However, Marciniak *et al.* demonstrated, through deuteration experiments, that the catalyst  $\text{RuHCl}(\text{CO})(\text{PCy}_3)_3$  **335** derived from the Grubbs I catalyst favors a *trans*-borylation process rather than the olefin metathesis (**Scheme 134**).<sup>[115a]</sup> Such reactivity could be interesting to test on methylene *exo*-glycal substrates.



**Scheme 134:** *trans*-borylation of alkene (a) opposed to olefin metathesis (b).

The borylation of an enol ether has also been reported using a C-H activation strategy. Our attempt at adapting this procedure to a methylene *exo*-glycal substrate proved unproductive. It might be more convenient to use instead halogenated substrates **336**. Such compounds have been previously reported as a result of Wittig or modified Julia reactions, and would open the door for alternative synthetic methods such as the Miyaura borylation or the metal/halogen exchange (**Scheme 135**).

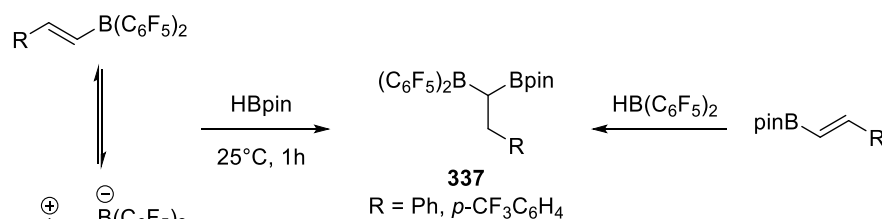


**Scheme 135:** Proposed borylation of halogenated *exo*-glycals.

## 8.2. Boron-Wittig and Peterson olefinations of sugar lactones

For both the boron-Wittig and the Peterson reaction, the borylated reagents, respectively the *gem*-bisborylmethane **121** and the *gem*-silylborylmethane **122**, were already described and used to efficiently convert aldehydes and ketones. However, when these reactions were carried out on ester substrates, such as lactones, deborylation was observed. This was the result of a ring opening followed by the hydrolysis of the boronate moiety.

During our exploration of the boron-Wittig reaction conditions, this side reactivity could not be prevented even though we put in motion several strategies to avoid the ring opening process through the lactone modifications, or the change of boron group's nature to resist its hydrolysis. Thus, instead of trying to disfavor the side-reactivity, we put our efforts into encouraging the desired process. Enhancing the nucleophilicity of the alkoxide intermediate by trapping or modifying its counteranion did not succeed. The elimination step could also be facilitated using more electrophilic borylated moieties. The synthesis of a perfluoro Bpin group failed, but Stephan *et al.* reported the syntheses of unsymmetrical *gem*-bisboryllakanes **337** that could display the suitable reactivity (**Scheme 136**).<sup>[198]</sup>



**Scheme 136:** Reported synthesis of asymmetrical B(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>/Bpin reagent.

In a step-by-step approach, we demonstrated the nucleophilicity of the deprotonated reagent **121**, but the alkoxide resulting from its attack on the lactone substrate could not be trapped and identified.

In contrast to the boron-Wittig reaction, the use of the Peterson olefination for the synthesis of borylated alkenes has been less explored. More specifically, the factors behind the chemoselectivity between the elimination of the boryl or silyl moiety were unclear. We carried out an experimental and theoretical study to improve our comprehension of this reaction.

The reaction between the TMS/Bpin reagent **122** and benzaldehyde was optimized. These reaction conditions were subsequently applied to seventeen aldehydes and ketones. It transpired that chemoselectivity totally favored the Peterson olefination. It is also interesting to note that the corresponding borylated olefins were obtained in a *Z/E* ratio from 2:1 to 6:1 whereas reported olefination methods provide preferentially *E*-vinyl boronates (see chapter 1.2.2., page 20). Our experimental results were supported by a theoretical mechanism explored by computational means.

To study the influence of the borylated/silylated groups' nature, a library of *gem*-silylborylmethanes was constituted (**Figure 35**). It is interesting to mention that most of these reagents are reported here for the first time. Their reaction with benzaldehyde was then carried out under our optimized conditions. While the modifications of the borylated group proved mostly ineffective, the various silylated groups put to light the influence of their steric and electronic effects on the chemoselectivity. Unfortunately, this work did not allow us to identify a boryl/silyl



combination more efficient than TMS/Bpin to perform our olefination reactions.

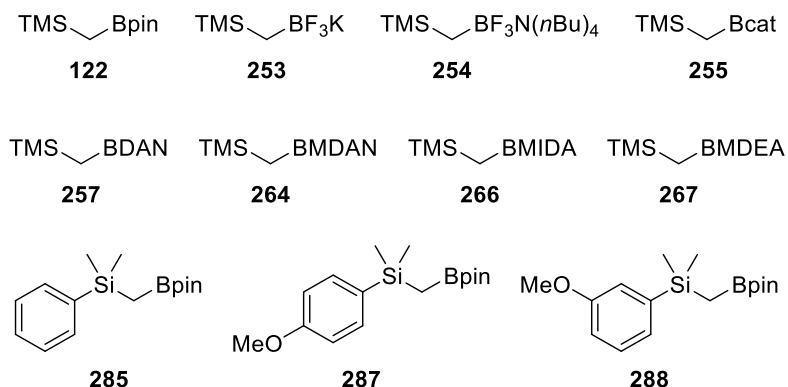
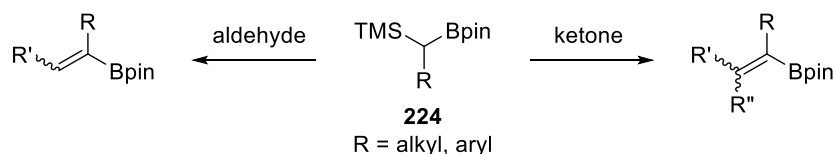


**Figure 35:** Variation of the borylated and silylated groups.

A further development of our study would be the functionalization of the central carbon of the *gem*-silylborylmethane reagents **224** (Scheme 137). Their reaction with aldehydes would lead to trisubstituted borylated olefins with a different substitution pattern. If the reaction is applied to ketone substrates instead, it would constitute the first report of the formation of tetrasubstituted alkenylboronates *via* a Peterson olefination.



**Scheme 137:** Peterson olefination using substituted *gem*-silylborylmethane.

Moving from aldehyde and ketone substrates to esters and lactones is often a challenging step. While this issue was extensively studied for the boron-Wittig reaction, the Peterson olefination of these substrates needs to be deepened. For the Peterson and boron-Wittig olefinations alike, a solution could be to supply enough energy to the reaction, through heating, to overcome the energetic barrier of the elimination step. The inspiration for this is the Wittig reaction on lactone, as it was reported to require heating the mixture above the solvent boiling point, which prompted the use of a steel vessel to withstand the pressure building up in the process.

### 8.3. Wittig and modified Julia olefinations of sugar lactones

Synthetic methods based on the Wittig or the modified Julia olefinations have been successfully exploited in the field of *exo*-glycals chemistry. However, unlike the boron-Wittig and the Peterson olefination, these reactions have not been reported for the synthesis of borylated alkenes. Moreover, the necessary  $\alpha$ -borylphosphonium **123** reagent has only been reported once,<sup>[189]</sup> and the  $\alpha$ -borylsulfone **124** has never been described (**Figure 36**). Our efforts were focused on the synthesis of such adequate reagents.

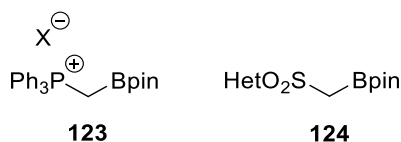


**Figure 36:** borylated phosphonium and sulfone reagents.

Our initial approach for the synthesis of  $\alpha$ -borylphosphonium **123** was the nucleophilic substitution of triphenylphosphine onto  $\alpha$ -halogenoboronate. Although the desired phosphonium salts were obtained, they proved unstable, as the halide counteranion brought about the deborylation of the molecule. This observation allowed us to challenge the misleading conclusion of Srebnik *et al.*<sup>[189]</sup> Nevertheless, this reagent was used in the olefination of benzaldehyde and afforded the corresponding borylated styrene in low yields. This represents the first example of the synthesis of a vinylboronate via a Wittig reaction.

Additional efforts were made to synthesize more stable  $\alpha$ -borylphosphonium derivatives by modifying the borylated group for a more robust one, less prone to the complexation by a halide. The BMIDA derivative couldn't be obtained, and the BF<sub>3</sub>K compound proved to be insoluble. The variation of the counteranion was also explored and motivated us to investigate another synthetic route, involving the borylation of methylphosphonium triflate. This strategy showed encouraging results and should be pursued further.

Finally, the synthesis of  $\alpha$ -borylsulfone **124** was attempted. To avoid an oxidation step in presence of a boron group, we prioritized the

borylation of a benzothiazole (BT) or phenyltetrazole (PT) methylsulfone. However, we couldn't prevent the autocondensation phenomenon that occurred under these conditions. Alternative synthetic routes were consequently explored, with modified reaction sequences. The borylation of an  $\alpha$ -halogenothioether is a promising approach that should be continued in priority. If needed, boron group more robust than Bpin could be used to better cope with the subsequent oxidation step.<sup>[199]</sup> While such borylated group render the previous boron-Wittig, Peterson or Wittig reagents insoluble in THF or too difficult to deprotonated, we envisioned that the sulfone moiety would enhance the solubility of the molecule and lower its central protons'  $pK_a$ .

Once these borylated phosphonium and sulfone reagents are synthesized, their exploitation for the synthesis of vinylboronates through a Wittig or modified Julia olefination respectively should be investigated. Initial work on aldehydes and ketones would constitute a significant advance in this field of organic chemistry, and further studies might be conducted on esters, lactones, and finally sugar lactones, which could lead to the synthesis of the first borylated *exo*-glycal.

#### 8.4. General conclusion

The synthesis of borylated *exo*-glycals was not achieved within this thesis, but the appeal of such compounds remains intact.

Across all the chapters of this thesis, optimization efforts were conducted following a "one variable at a time" (OVAT) approach, which allowed for the investigation of the influence of each parameter on the reactivity. Another possible strategy is the "design of experiment" (DoE) method, where multiple features are modified in every experiment. Using this approach, reaction optimizations could have been accelerated. Furthermore, the key to a successful transformation could emerge from the combined effect of several parameters, which was lost in our OVAT attitude.

Our approach based on the borylation of methylene *exo*-glycals was admittedly shallow, but it put to light that such a transformation will require extensive researches, far beyond the simple replication of reported

procedures. The work demanded to develop a catalytic system suited for the borylation of methylene *exo*-glycal is considerable and would be more adapted to a research group with expertise in palladium chemistry. A total investment in this approach would likely have prevented us to explore other strategies during this thesis.

In contrast, the olefination of sugar lactone was explored broadly. As a result of our work, the boron-Wittig was found incapable to perform the olefination of lactones. Even if the use of more electron deficient boron moiety still represents a promising strategy (**Scheme 136**), the instability of such compounds would constitute a major drawback and would limit the reach of this method.

The Peterson olefination of aldehydes and ketones, and its mechanism, was also well studied in this thesis. The conclusions of this experimental and theoretical work may prove useful not only in the continuation of our work on lactones, but also to other research group using *gem*-silylborylalkanes. Regarding the Peterson olefination of lactones, although the number of experiments reported in this thesis is limited, it transpires that this transformation is not straightforward and the prospect of this method is grim.

On the other hand, the Wittig and the modified Julia reactions are our most auspicious leads. The synthesis of the corresponding reagents could not be completed during this thesis (**Figure 36**), but some promising routes remain to be investigated. The borylated sulfones **124**, in particular, still hold many promises, as it is expected to solve some of the issues encountered with borylated phosphoniums **123** (insoluble or prone to deborylation). The synthesis of vinylboronate via a Wittig or modified Julia reaction would constitute a novel and attractive method, worthy of the attention of the organic chemistry community. Furthermore, these reactions are compatible with esters and sugar lactones, and should be made a priority by anyone interested in achieving the synthesis of borylated *exo*-glycals.

## 9. Experimental section

### 9.1. General

**Solvents:** All solvents (for reactions, extractions and purification by chromatography) were obtained from commercial sources and used without further purification, unless mentioned otherwise.

**Reactants and reagents:** Commercially available reagents were used as purchased, except for the triethylamine and the tetramethylpiperidine that were distilled before use.

**Temperatures:** The reactions requiring a temperature higher than room temperature were carried out using a silicon oil bath. The temperature was controlled by a temperature probe. The reactions requiring a temperature of -78°C were carried out using an acetone/dry ice bath. The temperature of 0°C was achieved with the use of ice baths.

**Anhydrous conditions:** Reactions requiring anhydrous conditions were performed in anhydrous grade solvents in glassware previously flame-dried by a Bunsen burner under reduced pressure and then cooled down under argon atmosphere.

**Thin layer chromatography (TLCs):** TLCs were carried out on Merck Silica gel 60 F254 Aluminum backed plates using UV light and potassium permanganate for revelation.

**Flash chromatography:** Flash chromatography was performed using Merck Silica gel 60Å (40-63 µm), or Merk Aluminum oxide 90 active neutral (63-200 µm).

**Nuclear Magnetic Resonance (NMR) spectroscopy:** NMR spectra were recorded on a *Bruker avance II 300* operating at 300 MHz for proton-<sup>1</sup>H and 75 MHz for carbon-<sup>13</sup>C, on a *Bruker Avance 500* spectrometer operating at 500 MHz for proton-<sup>1</sup>H, 125 MHz for carbon-<sup>13</sup>C and 160 MHz for boron-<sup>11</sup>B or on a *Jeol JNM-ECZL G series* spectrometer operating at 600 MHz for proton-<sup>1</sup>H, 151 MHz for carbon-<sup>13</sup>C and 193 MHz for boron-<sup>11</sup>B. All NMR experiments were carried out in tubes made of borosilicate glass. The recorded <sup>13</sup>C NMR spectra were proton-decoupled. In many cases, the carbon α to the boron was not found due to quadrupolar effect.<sup>[200]</sup> NMR

multiplicities are abbreviated as follow: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet.

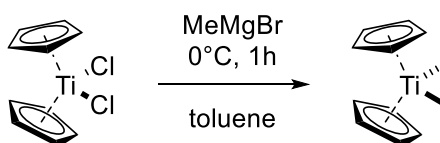
Solvents are indicated case-by-case. Chemical shifts ( $\delta$ ) are reported in ppm relative to the reference signal ( $\text{CHCl}_3$  at 7.16 ppm for  $^1\text{H}$  NMR and  $\text{CDCl}_3$  77.16 ppm for  $^{13}\text{C}$  NMR,  $\text{CD}_2\text{HCN}$  at 1.94 ppm for  $^1\text{H}$  NMR and  $\text{CD}_3\text{CN}$  1.32 ppm for  $^{13}\text{C}$  NMR,  $\text{C}_2\text{HD}_5\text{SO}$  at 2.50 ppm for  $^1\text{H}$  NMR,  $\text{C}_2\text{HD}_5\text{CO}$  at 2.05 ppm for  $^1\text{H}$  NMR and  $(\text{CD}_3)_2\text{CO}$  29.84 ppm for  $^{13}\text{C}$  NMR) and coupling constants are given in Hertz (Hz).

The  $^1\text{H}$  NMR yields were measured using dimethyl terephthalate (DMT) as an internal standard. Precisely weighted amounts of the crude product (*ca* 5 mg) and DMT (5-10 mg) were dissolved in 0.5 ml of the deuterated solvent. A  $^1\text{H}$  NMR experiment was then performed with the relaxation time set at 10 seconds. The NMR yields were calculated from the integration ratio between the internal standard (based on the 8.10 ppm peak) and the product (based on the signal of characteristic protons, such as the position 1 of molecules **222**, **234-249**).

**Mass spectrometry:** Mass spectra and high-resolution mass spectra were recorded by the ASM platform of the UCLouvain on a *Thermo Orbitrap Exactive* device. The mass values are given in Dalton.

## 9.2. Procedures and compounds characterization

### Dimethyltitanocene (**15**)



In a dry round-bottom flask under inert atmosphere, bis(cyclopentadienyl)titanium (IV) dichloride (1.000 g, 4.02 mmol, 1 eq.) was suspended in 10 ml of dry toluene and the mixture was cooled to 0°C. Then a 22% solution of methylmagnesium chloride in THF (3.10 ml, 9.30 mmol, 2.3 eq.) was added dropwise and the reaction mixture is stirred for one hour at 0°C. The reaction was quenched with a 6% solution of  $\text{NH}_4\text{Cl}$

and stirred for an additional 15 minutes. The mixture was filtered through a pad of celite and added to a separatory funnel containing water and toluene. The organic layer was washed three times with cold water and cold brine, dried over  $\text{MgSO}_4$ , and evaporated under reduced pressure without heating the solution above  $40^\circ$  until an estimated volume of 5-10 ml remains. The resulting mixture was assayed by  $^1\text{H}$  NMR to determine the concentration. The product **15** (7.6% w/w, 9.755 g, 89%) is obtained as an orange solution.

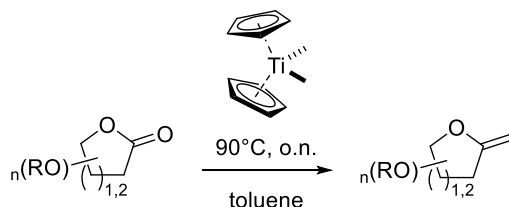


Chemical Formula:  $\text{C}_{12}\text{H}_{16}\text{Ti}$   
Molecular Weight: 208,13

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.04 (s, 10H,  $\text{H}^1$ ), -0.15 (s, 6H,  $\text{H}^2$ ).

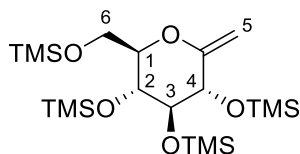
The description of this compound matches the one previously reported in literature.<sup>[28]</sup>

#### General methylenation procedure (133-135)



In a dry round-bottom flask equipped with a condenser and under inert atmosphere, the sugar lactone (420 mg, 0.90 mmol, 1.0 eq.) was dissolved in 15 ml of dry toluene. A solution of dimethyltitanocene **15** in toluene (15.5% w/w, 2.051g, 1.53 mmol, 1.7 eq.) was added and the reaction mixture was stirred overnight at  $90^\circ\text{C}$ . The mixture was cooled down to room temperature, concentrated under reduced pressure and purified by chromatography on alumina gel to give the corresponding methylene *exo*-glycal **133-135**.

((*(3R,4S,5R,6R)*-2-methylene-6-(((trimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl)tris(oxy))tris(trimethylsilane) (**133**)



Chemical Formula: C<sub>19</sub>H<sub>44</sub>O<sub>5</sub>Si<sub>4</sub>  
Molecular Weight: 464,90

Quantity: 301 mg

Aspect: light-yellow oil

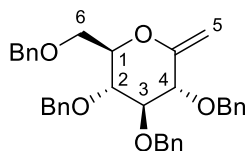
Purification: flash chromatography on alumina (95:5 *n*-hexane/AcOEt)

Isolated yield: 72%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 4.59 (dd, *J* = 1.4, 0.6 Hz, 1H, H<sup>5a</sup>), 4.47 (dd, *J* = 1.5, 0.6 Hz, 1H, H<sup>5b</sup>), 3.83 (dd, *J* = 11.6, 1.9 Hz, 1H, H<sup>3</sup>), 3.77 (dt, *J* = 7.7, 1.4 Hz, 1H, H<sup>4</sup>), 3.71 (dd, *J* = 11.7, 4.3 Hz, 1H, H<sup>2</sup>), 3.60 (dd, *J* = 9.5, 7.7 Hz, 1H, H<sup>1</sup>), 3.52 – 3.38 (m, 2H, H<sup>6</sup>), 0.17 (s, 9H, H<sup>TMS</sup>), 0.17 (s, 9H, H<sup>TMS</sup>), 0.16 (s, 9H, H<sup>TMS</sup>), 0.13 (s, 9H, H<sup>TMS</sup>).

The description of this compound matches the one previously reported in literature.<sup>[26]</sup>

((*(2R,3R,4S,5R)*-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-methylenetetrahydro-2*H*-pyran (**134**)



Chemical Formula: C<sub>35</sub>H<sub>36</sub>O<sub>5</sub>  
Molecular Weight: 536,67



Quantity: 352 mg

Aspect: light-yellow oil

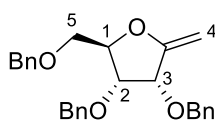
Purification: flash chromatography on alumina (95:5 *n*-hexane/AcOEt)

Isolated yield: 64%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.38 – 7.09 (m, 20H, H<sup>arom</sup>), δ 4.86 (d, *J* = 11.2 Hz, 1H, H<sup>Bn</sup>), 4.82 – 4.73 (m, 3H, H<sup>Bn,5a</sup>), 4.72 (d, *J* = 11.2 Hz, 1H, H<sup>Bn</sup>), 4.65 (d, *J* = 11.5 Hz, 1H, H<sup>Bn</sup>), 4.64 – 4.62 (m, 2H, H<sup>Bn, 5b</sup>), 4.53 (d, *J* = 12.2 Hz, 1H, H<sup>Bn</sup>), 4.50 (d, *J* = 10.9 Hz, 1H, H<sup>Bn</sup>), 3.96 (dt, *J* = 7.6, 1.4 Hz, 1H, H<sup>4</sup>), 3.83 – 3.63 (m, 5H, H<sup>1,2,3,6</sup>).

The description of this compound matches the one previously reported in literature.<sup>[201]</sup>

(2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-methylenetetrahydrofuran (**135**)



Chemical Formula: C<sub>27</sub>H<sub>28</sub>O<sub>4</sub>  
Molecular Weight: 416,52

Quantity: 332 mg

Aspect: light-yellow oil

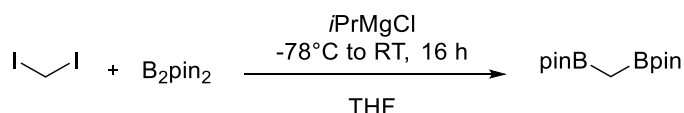
Purification: flash chromatography on alumina (90:10 *n*-hexane/AcOEt)

Isolated yield: 78%

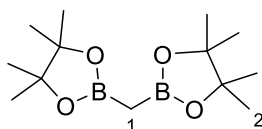
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.41 – 7.22 (m, 15H, H<sup>arom</sup>), 4.75 (d, *J* = 12.1 Hz, 1H, H<sup>Bn</sup>), 4.61 (d, *J* = 11.9 Hz, 1H, H<sup>Bn</sup>), 4.58 (d, *J* = 12.1 Hz, 1H, H<sup>Bn</sup>), 4.55 (d, *J* = 12.2 Hz, 1H, H<sup>Bn</sup>), 4.53 – 4.47 (m, 3H, H<sup>4a,1,Bn</sup>), 4.47 (d, *J* = 11.8 Hz, 1H, H<sup>Bn</sup>), 4.20 (d, *J* = 4.7 Hz, 1H, H<sup>3</sup>), 4.13 (dd, *J* = 1.8, 0.7 Hz, 1H, H<sup>4b</sup>), 3.97 (dd, *J* = 7.1, 4.7 Hz, 1H, H<sup>2</sup>), 3.71 (dd, *J* = 11.2, 2.8 Hz, 1H, H<sup>5a</sup>), 3.56 (dd, *J* = 11.2, 4.4 Hz, 1H, H<sup>5b</sup>).

The description of this compound matches the one previously reported in literature.<sup>[202]</sup>

#### Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (**121**)



In a dry round-bottom flask under inert atmosphere, the bispinacolatodiboron (2.800 g, 11.03 mmol, 1.0 eq.) and the diiodomethane (4.10 ml, 50.85 mmol, 4.6 eq.) are dissolved in 20 ml of dry THF. The mixture is cooled to -78°C, then the turbo Grignard reagent (25.00 ml, 2M, 50.00 mmol, 4.5 eq.) is added dropwise to the mixture through an addition funnel. The funnel is rinsed with 5 ml of anhydrous THF, then the solution is allowed to return to RT overnight. The reaction is quenched by NH<sub>4</sub>Cl, the layers are separated and the aqueous phase is extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product is purified by flash chromatography (from 95:5 to 90:10 *n*-hexane/AcOEt) to yield **121** (2.046 g, 69%) as light-yellow crystals.



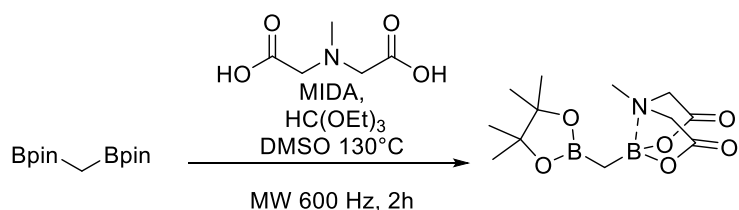
Chemical Formula: C<sub>13</sub>H<sub>26</sub>B<sub>2</sub>O<sub>4</sub>  
Molecular Weight: 267,97

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 1.23 (s, 24H, H<sup>2</sup>), 0.35 (s, 2 H, H<sup>1</sup>).

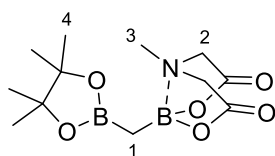
$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  83.0, 24.7. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

The description of this compound matches the one previously reported in literature.<sup>[139]</sup>

4-methyl-8-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)dihydro-4 $\lambda^4$ ,8 $\lambda^4$ -[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborole-2,6(3*H*,5*H*)-dione (**160**)



In a thick-walled tube, the bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **121** (464 mg, 1.73 mmol, 1.0 eq.), the N-methyliminodiacetic acid (1.530 g, 10.40 mmol, 6.0 eq.), and the triethyl orthoformate (1.16 ml, 6.97 mmol, 4.0 eq.) are placed in 6 ml of DMSO. The tube is flushed with argon, sealed and placed in the microwave at 130°C for 2 hours. Distilled water is added, and the crude mixture is extracted three times with AcOEt. The combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product is purified by flash chromatography (from 90:10 to 0:100 *n*-hexane/AcOEt) to yield **160** (177 mg, 34%) as a white solid.

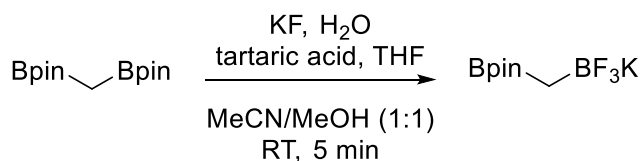


Chemical Formula:  $\text{C}_{12}\text{H}_{21}\text{B}_2\text{NO}_6$   
Molecular Weight: 296,92

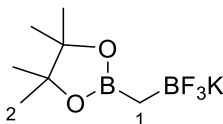
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.91 (d,  $J$  = 16.1 Hz, 2H,  $\text{H}^{2a}$ ), 3.76 (d,  $J$  = 16.1 Hz, 2H,  $\text{H}^{2b}$ ), 3.00 (s, 3H,  $\text{H}^3$ ), 1.23 (s, 12H,  $\text{H}^4$ ), 0.28 (s, 2H,  $\text{H}^1$ )

The description of this compound matches the one previously reported in literature.<sup>[143]</sup>

Potassium trifluoro((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)borate (**166**)



In a round-bottom flask, the bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **121** (590 mg, 2.20 mmol, 1.0 eq.) is dissolved in 16 ml of a 1:1 mix of methanol and acetonitrile. To this solution are added the potassium fluoride (511 mg, 8.80 mmol, 4.0 eq.) in 1.2 ml of distilled water and, after three minutes, the tartaric acid (660 mg, 4.40 mmol, 2.0 eq.) dissolved in 4 ml of THF. After five minutes, the mixture is filtered on a Büchner funnel, and the solid is washed with 20 ml of MeCN. The filtrate is concentrated under reduced pressure to yield **166** (214 mg, 41%) as a white solid.

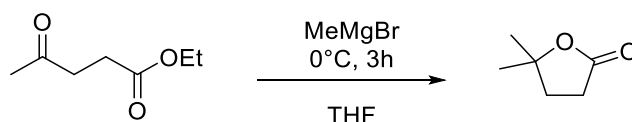


Chemical Formula:  $\text{C}_7\text{H}_{14}\text{B}_2\text{F}_3\text{KO}_2$   
Molecular Weight: 247,90

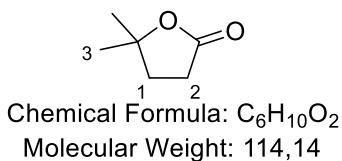
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  1.09 (s, 12H,  $\text{H}^2$ ), -0.62 (s, 2H,  $\text{H}^1$ ).

The description of this compound matches the one previously reported in literature.<sup>[145]</sup>

5,5-dimethyldihydrofuran-2(3*H*)-one (**170**)



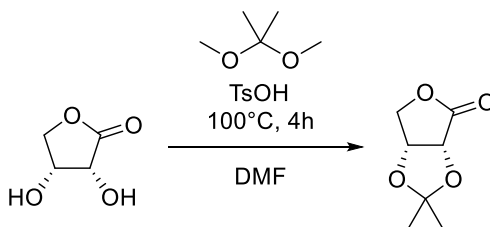
In a dry round-bottom flask under inert atmosphere, the ethyl levulinate (2.00 ml, 14.01 mmol, 1.0 eq.) is dissolved in 15 ml of dry THF. The mixture is cooled to 0°C, then the Grignard (5.00 ml, 3 M, 15.00 mmol, 1.1 eq.) is added dropwise and the mixture is stirred three hours at this temperature. The reaction is quenched by the addition of saturated NH<sub>4</sub>Cl solution. The layers are separated and the aqueous one is extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product is purified by flash chromatography (70:30 *n*-hexane/AcOEt) to yield **170** (314 mg, 20%) as a colourless oil.



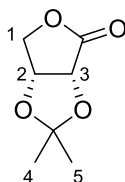
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.62 (dd, *J* = 8.6, 7.8 Hz, 2H, H<sup>2</sup>), 2.06 (dd, *J* = 8.6, 7.9 Hz, 2H, H<sup>1</sup>), 1.44 (s, 6H, H<sup>3</sup>).

The description of this compound matches the one previously reported in literature.<sup>[156]</sup>

(3*aR*,6*aR*)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3*aH*)-one (**172**)



In a round-bottom flask equipped with a condenser, the erythrolactone (947 mg, 8.02 mmol, 1.0 eq.), the *p*TSA (40 mg, 0.21 mmol, 3 mol%), and the 2,2-dimethoxy propane (8.00 ml, 65.14 mmol, 8.1 eq.) are dissolved in 10 ml of DMF. The mixture is refluxed at 100°C for four hours. Upon returning to RT, 1 ml of saturated NaHCO<sub>3</sub> is added, then the dimethoxy propane is evaporated under reduced pressure. Distilled water is added to the crude mixture, the layers are separated and the aqueous one is extracted three times with DCM. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product is purified by flash chromatography (from 90:10 to 70:30 *n*-hexane/AcOEt) to yield **172** (183 mg, 14%) as a white solid.

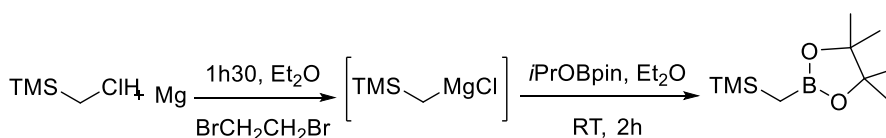


Chemical Formula: C<sub>7</sub>H<sub>10</sub>O<sub>4</sub>  
Molecular Weight: 158,15

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.88 (ddd, *J* = 5.7, 3.7, 0.8 Hz, 1H, H<sup>1a</sup>), 4.75 (d, *J* = 5.7 Hz, 1H, H<sup>1b</sup>), 4.48 (dt, *J* = 11.0, 0.6 Hz, 1H, H<sup>2</sup>), 4.41 (dd, *J* = 11.0, 3.7 Hz, 1H, H<sup>3</sup>), 1.50 (d, *J* = 0.7 Hz, 3H, H<sup>4 or 5</sup>), 1.41 (d, *J* = 0.7 Hz, 3H, H<sup>5 or 4</sup>).

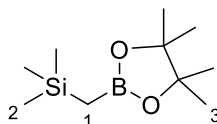
The description of this compound matches the one previously reported in literature.<sup>[157]</sup>

Trimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane  
(**122**)



In a dry round-bottom flask equipped with a condenser, under inert atmosphere, magnesium turnings (1.000 g, 41.14 mmol, 1.4 eq.) are placed in 20 ml of dry diethyl ether. A drop of 1,2-dibromoethane is added to

activate the magnesium. The (chloromethyl)trimethylsilane (4.00 ml, 28.66 mmol, 1.0 eq.), as a solution in 12 ml of dry diethyl ether, is added by portions under reflux. Once the solution turns turbid, it is stirred for an additional 1h30 at RT. In a second dried flask, the *i*PrOBpin (6.00 ml, 29.41 mmol, 1.0 eq.) is dissolved in 12 ml of dry diethyl ether. The prepared Grignard is added slowly to this solution. The reaction mixture is stirred 2h at RT. The mixture is cooled to 0°C, then the reaction is quenched by the addition of saturated NH<sub>4</sub>Cl solution. The layers are separated and the aqueous one is extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product is purified by distillation under reduced pressure at 70°C, to yield **122** (5.587 g, 91%) as a colourless oil.



Chemical Formula: C<sub>10</sub>H<sub>23</sub>BO<sub>2</sub>Si

Molecular Weight: 214.19

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.24 (s, 12H, H<sup>3</sup>), 0.10 (s, 2H, H<sup>1</sup>), 0.05 (s, 9H, H<sup>2</sup>).

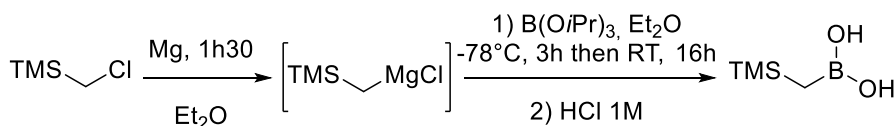
<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 82.8, 25.1, 0.5. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

<sup>11</sup>B NMR (160 MHz, CDCl<sub>3</sub>) δ 34.14.

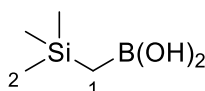
HRMS (ESI) m/z: [M + H]<sup>+</sup> Calcd for C<sub>10</sub>H<sub>24</sub>O<sub>2</sub>BSi 215.1639; Found 215.1631.

The description of this compound matches the one previously reported in literature.<sup>[167]</sup>

((Trimethylsilyl)methyl)boronic acid (**218**)



In a dry round-bottom flask equipped with a condenser, under inert atmosphere, magnesium turnings (1.000 g, 41.14 mmol, 1.6 eq.) are placed in 20 ml of dry diethyl ether. A drop of 1,2-dibromoethane is added to activate the magnesium. The (chloromethyl)trimethylsilane (4.00 ml, 28.66 mmol, 1.1 eq.), as a solution in 12 ml of dry diethyl ether, is added by portions under reflux. Once the solution turns turbid, it is stirred for an additional 1h30 at RT. In a second dried flask, the B(OiPr)<sub>3</sub> (6.00 ml, 26.00 mmol, 1.0 eq.) is dissolved in 12 ml of dry diethyl ether. The prepared Grignard is added slowly to this solution. The reaction mixture is stirred 3h at -78°C, then slowly warmed up to RT overnight. The reaction is quenched by the addition of HCl 1M. The layers are separated and the aqueous one is extracted three times with a diethyl ether/ DCM mixture (4:1). The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure to yield **218** (2.535 g, 74%) as white crystals.



Chemical Formula: C<sub>4</sub>H<sub>13</sub>BO<sub>2</sub>Si

Molecular Weight: 132.04

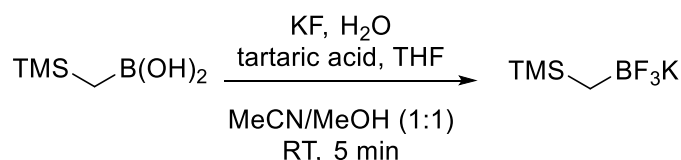
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 0.27 (s, 2H, H<sup>1</sup>), 0.06 (s, 9H, H<sup>2</sup>). For the trimeric form: δ 0.35 (s, 2H, H<sup>1</sup>), 0.07 (s, 9H, H<sup>2</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)** δ 0.77, 0.56 One signal corresponds to the monomeric form, the other one to the trimeric form. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

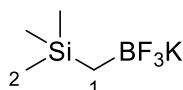
**<sup>11</sup>B NMR (160 MHz, CDCl<sub>3</sub>)** δ 33.3, 31.2. One signal corresponds to the monomeric form, the other one to the trimeric form.



Potassium (trimethylsilyl)methyltrifluoroborate (**253**)



In a round-bottom flask, the boronic acid **218** (1.316 g, 6.14 mmol, 1.0 eq.) is dissolved in 42 ml of a 1:1 mixture of methanol and acetonitrile. To this solution are added the potassium fluoride (1.430 g, 24.61 mmol, 4.0 eq.) in 3.5 ml of distilled water and, after three minutes, the tartaric acid (1.850 g, 12.33 mmol, 2.0 eq.) dissolved in 11 ml of THF. After five minutes, the mixture is filtered on a Büchner funnel, and the solid is washed with 40 ml of MeCN. The filtrate is concentrated under reduced pressure to yield **253** (1.156 g, 97%) as a white solid.



Chemical Formula:  $\text{C}_4\text{H}_{11}\text{BF}_3\text{KSi}$

Molecular Weight: 194.12

**$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ )**  $\delta$  -0.09 (s, 9H,  $\text{H}^2$ ), -0.71 (bs, 2H,  $\text{H}^1$ ).

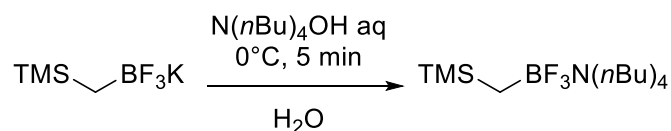
**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CD}_3\text{CN}$ )** was carried out, but no signals were observed. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect, and the TMS signal was overlapping with the solvent signal.

**$^{11}\text{B}$  NMR (160 MHz,  $\text{CD}_3\text{CN}$ )**  $\delta$  5.62 (q,  $J$  = 64.9 Hz).

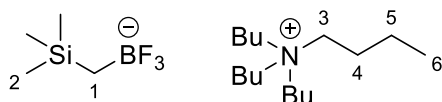
**HRMS (ESI)**  $m/z$ :  $[\text{M}]^-$  Calcd for  $\text{C}_4\text{H}_{11}\text{BF}_3\text{Si}$  155.0675; Found 155.0676.

The description of this compound matches the one previously reported in literature.<sup>[203]</sup>

Tetrabutylammonium (trimethylsilyl)methyltrifluoroborate (**254**)



In a round-bottom flask, the trifluoroborate **253** (400 mg, 2.06 mmol, 1.0 eq.) is dissolved in 5 ml of water. The solution is cooled down to 0°C and tetrabutylammonium hydroxide (1.350 g, 40% w/w, 2.00 mmol, 1.0 eq.) is added. After 5 minutes, the solution is extracted 3 times with DCM, the combined organic phases are dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield **254** (596 mg, 24%) as an off-white solid.



Chemical Formula: C<sub>20</sub>H<sub>47</sub>BF<sub>3</sub>SiN

Molecular Weight: 397.49

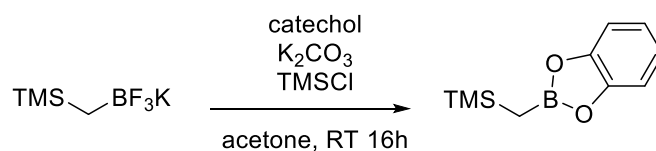
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 3.32 – 3.16 (m, 8H, H<sup>3</sup>), 1.73 – 1.54 (m, 8H, H<sup>4</sup>), 1.53 – 1.33 (m, 8H, H<sup>5</sup>), 1.00 (t, J = 7.3 Hz, 12H, H<sup>6</sup>), -0.02 (s, 9H, H<sup>2</sup>), -0.52 (q, J = 8.5 Hz, 2H, H<sup>1</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)** δ 58.9, 24.1, 19.9, 13.8, 1.2. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

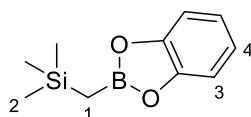
**<sup>11</sup>B NMR (160 MHz, CDCl<sub>3</sub>)** δ 5.89.

**HRMS (ESI)** m/z: [M]<sup>-</sup> Calcd for C<sub>4</sub>H<sub>11</sub>BF<sub>3</sub>Si 155.0675; Found 155.0676. [M]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>36</sub>N 242.2848; Found 242.2847.

(Benzo[d][1,3,2]dioxaborol-2-ylmethyl)trimethylsilane (**255**)



In a round-bottom flask, the trifluoroborate **253** (958 mg, 4.93 mmol, 1.0 eq.) is dissolved in 14 ml of acetone. The catechol (598 mg, 5.43 mmol, 1.1 eq.), the potassium carbonate (1.365 g, 9.88 mmol, 2.0 eq.) and the TMSCl (1.90 ml, 14.97 mmol, 3.0 eq.) are added. The reaction is stirred for 16h at room temperature. The solvent is evaporated and the solid is washed with DCM. The liquid phase is concentrated under reduced pressure to obtain **255** (235 mg, 23%) as a yellow oil.



Chemical Formula: C<sub>10</sub>H<sub>15</sub>BO<sub>2</sub>Si  
Molecular Weight: 206.12

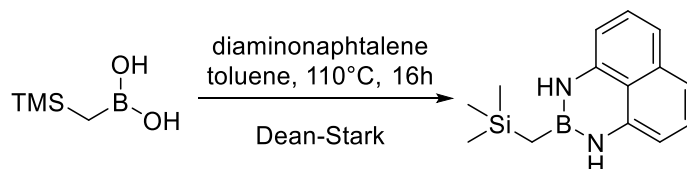
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.18 (m, 2H, H<sup>4</sup>), 7.04 (m, 2H, H<sup>3</sup>), 0.64 (s, 2H, H<sup>1</sup>), 0.11 (s, 9H, H<sup>2</sup>).

<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 148.7, 122.3, 112.1, 0.4. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

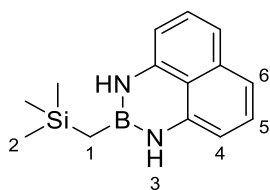
<sup>11</sup>B NMR (160 MHz, CDCl<sub>3</sub>) δ 35.85.

The HRMS analysis could not be performed due to the instability of the compound.

2-((Trimethylsilyl)methyl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (**257**)



In a round-bottom flask equipped with a Dean-Stark apparatus, the boronic acid **218** (1.400 g, 10.60 mmol, 1.0 eq.) and the diaminonaphthalene (2.516 g, 15.90 mmol, 1.5 eq.) are dissolved in 30 ml of toluene. The reaction is stirred for 16h at 110°C. The reaction is then cooled down to RT and quenched by the addition of water. The layers are separated and the aqueous one is extracted three times with AcOEt. The combined organic layers are washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. To remove the excess diaminonaphthalene, the crude mixture is taken up in DCM and washed with HCl 1M. The organic phase is collected and concentrated under reduced pressure to yield **257** (2.315 g, 86%) as a dark purple solid.



Chemical Formula: C<sub>14</sub>H<sub>19</sub>BN<sub>2</sub>Si  
Molecular Weight: 254.22

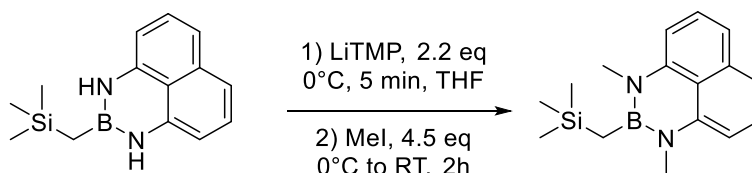
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.10 (dd, *J* = 8.3, 7.2 Hz, 2H, H<sup>5</sup>), 7.00 (dd, *J* = 8.3, 1.1 Hz, 2H, H<sup>6</sup>), 6.29 (dd, *J* = 7.3, 1.1 Hz, 2H, H<sup>4</sup>), 5.46 (bs, 2H, H<sup>3</sup>), 0.16 (s, 2H, H<sup>1</sup>), 0.09 (s, 9H, H<sup>2</sup>).

<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 141.5, 136.4, 127.7, 117.3, 105.4, 0.5. The signal of one of the aromatic carbons could not be found. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

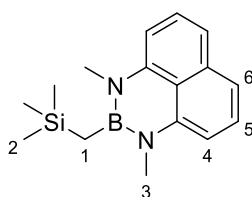
<sup>11</sup>B NMR (160 MHz, CDCl<sub>3</sub>) δ 32.17.

**HRMS (ESI)**  $m/z$ :  $[M]^+$  Calcd for  $C_{14}H_{19}N_2BSi$  255.1411; Found 254.1413.

1,3-Dimethyl-2-((trimethylsilyl)methyl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (**264**)



In a dry round-bottom flask, under inert atmosphere, tetramethylpiperidine (0.44 ml, 2.59 mmol, 2.2 eq.) is dissolved in 5 ml of dry THF. The solution is cooled down to 0°C and *n*-BuLi (1.03 ml, 2.5 M, 2.58 mmol, 2.2 eq.) is added dropwise. After 10 minutes, **257** (300 mg, 1.18 mmol, 1.0 eq.) is added as a solution in 1 ml of dry THF. The reaction is stirred for five additional minutes at 0°C before the iodomethane (0.33 ml, 5.30 mmol, 4.5 eq.) is added. The ice bath is removed, and the solution is stirred for 2h at RT. The reaction is quenched by the addition of water. The layers are separated and the aqueous one is extracted three times with AcOEt. The combined organic layers are washed with brine, dried over  $MgSO_4$  and concentrated under reduced pressure. The crude product is purified by flash chromatography (eluent: *n*-hexane) to yield **264** (240 mg, 85%) as a white solid.



Chemical Formula:  $C_{16}H_{23}BN_2Si$   
Molecular Weight: 282.27

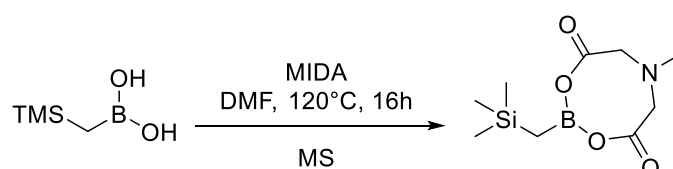
**$^1H$  NMR (300 MHz,  $CDCl_3$ )**  $\delta$  7.30 (t,  $J = 7.9$  Hz, 2H,  $H^5$ ), 7.16 (d,  $J = 8.1$  Hz, 2H,  $H^6$ ), 6.48 (d,  $J = 7.7$  Hz, 2H,  $H^4$ ), 3.07 (s, 6H,  $H^3$ ), 0.69 (s, 2H,  $H^1$ ), 0.11 (s, 9H,  $H^2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  143.1, 135.7, 127.3, 119.7, 117.6, 103.3, 35.3, 1.1. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

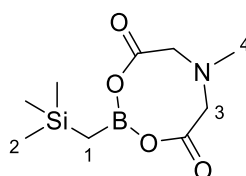
**$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )**  $\delta$  31.70.

**HRMS (APCI)**  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{16}\text{H}_{24}\text{BN}_2\text{Si}$  283.1802; Found 283.1802.

6-Methyl-2-((trimethylsilyl)methyl)-1,3,6,2-dioxazaborocane-4,8-dione (266)



In a round-bottom flask equipped with a condenser, the boronic acid **218** (500 mg, 3.78 mmol, 1.0 eq.), N-methyliminodiacetic acid (615 mg, 4.18 mmol, 1.1 eq.) and a spoon of molecular sieves are placed in 10 ml of DMF. The reaction is stirred for 16h at 120°C. Upon returning to RT, diethyl ether is added to trigger the precipitation of a white solid. This solid is filtered and washed with  $\text{Et}_2\text{O}$  to yield **266** (449 mg, 49%) as white crystals.



Chemical Formula:  $\text{C}_9\text{H}_{18}\text{BNO}_4\text{Si}$

Molecular Weight: 243,14

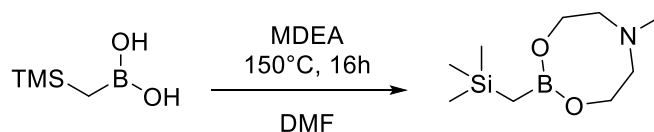
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  3.77 (d,  $J$  = 16.2 Hz, 2H,  $\text{H}^{3a}$ ), 3.62 (d,  $J$  = 16.2 Hz, 2H,  $\text{H}^{3b}$ ), 2.87 (s, 3H,  $\text{H}^4$ ), 0.09 (s, 9H,  $\text{H}^2$ ), -0.28 (s, 2H,  $\text{H}^1$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  166.9, 61.3, 46.0, 0.7. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

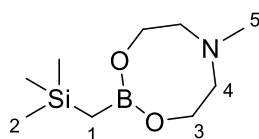
**$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )**  $\delta$  14.92.

**HRMS (ESI)**  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_9\text{H}_{18}\text{O}_4\text{BNNaSi}$  265.1027; Found 265.1026.

6-Methyl-2-((trimethylsilyl)methyl)-1,3,6,2-dioxazaborocane (**267**)



In a round-bottom flask equipped with a condenser, the boronic acid **218** (592 mg, 4.48 mmol, 1.0 eq.) and N-methyldiethanolamine (0.57 ml, 4.97 mmol, 1.1 eq.) are dissolved in 12 ml of DMF. The reaction is stirred for 16h at 150°C. The solution is cooled down to RT and the solvent is removed under reduced pressure. The solid which is obtained is dissolved in DCM and *n*-hexane is added to induce precipitation. The precipitate is filtered out, and the filtrate is concentrated under reduced pressure to yield **267** (429 mg, 45%) as a yellow oil.



Chemical Formula:  $\text{C}_9\text{H}_{22}\text{BNO}_2\text{Si}$

Molecular Weight: 215.18

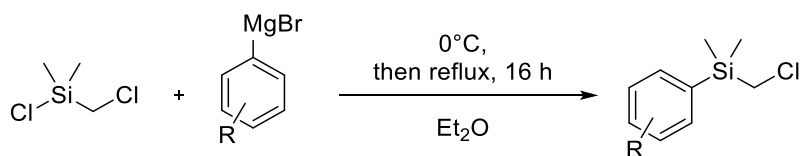
**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )**  $\delta$  3.92 (bs, 1H,  $\text{H}^{3a}$ ), 3.78 (bs, 1H,  $\text{H}^{3b}$ ), 2.96 (bs, 1H,  $\text{H}^{4a}$ ), 2.84 (bs, 1H,  $\text{H}^{4b}$ ), 2.62 (s, 3H,  $\text{H}^5$ ), 0.02 (s, 9H,  $\text{H}^2$ ), -0.48 (s, 2H,  $\text{H}^1$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ )**  $\delta$  60.9, 60.7, 46.7, 1.0. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**$^{11}\text{B}$  NMR (193 MHz,  $\text{CDCl}_3$ )**  $\delta$  14.17.

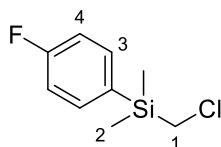
**HRMS (ESI)**  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_9\text{H}_{23}\text{O}_2\text{BNSi}$  216.1591; Found 216.1592.

### General procedure for $\alpha$ -chlorosilane (280-282)



In a dry round-bottom flask equipped with a condenser, under inert atmosphere, the chlorosilane (0.50 ml, 3.81 mmol, 1.0 eq.) is dissolved in 5 ml of dry diethyl ether, and the solution is cooled to 0°C. The Grignard reagent (5.00 ml, 0.8 M, 4.00 mmol, 1.1 eq.) is added dropwise, then the reaction is refluxed overnight. Upon returning to RT, the reaction is quenched by cold saturated  $\text{NH}_4\text{Cl}$ . The layers are separated and the aqueous one is extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

### (Chloromethyl)(4-fluorophenyl)dimethylsilane (280)



Chemical Formula:  $\text{C}_9\text{H}_{12}\text{ClFSi}$   
Molecular Weight: 202,73

Quantity: 584 mg

Aspect: yellow oil

Purification: filtration through a silica plug

Isolated yield: 76%

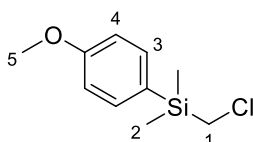
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (dd,  $J = 8.6, 6.1$  Hz, 2H,  $\text{H}^4$ ), 7.08 (dd,  $J = 9.3, 8.6$  Hz, 2H,  $\text{H}^3$ ), 2.93 (s, 2H,  $\text{H}^1$ ), 0.42 (s, 6H,  $\text{H}^2$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  165.2, 163.2, 135.9, 135.8, 131.7, 131.7, 115.4, 115.2, 30.4, -4.3.



**HRMS (ESI)** m/z: [M + Na]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>12</sub>ClFSiNa 225.0279; Found 225.0283.

(Chloromethyl)(4-methoxyphenyl)dimethylsilane (**281**)



Chemical Formula: C<sub>10</sub>H<sub>15</sub>ClOSi  
Molecular Weight: 214,76

Quantity: 511 mg

Aspect: colorless oil

Purification: flash chromatography on alumina (from 95:5 to 90:10 *n*-hexane/AcOEt)

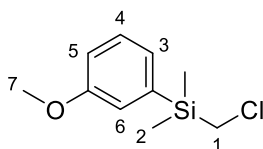
Isolated yield: 63%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.48 (d, *J* = 8.7 Hz, 2H, H<sup>4</sup>), 6.94 (d, *J* = 8.7 Hz, 2H, H<sup>3</sup>), 3.83 (s, 3H, H<sup>5</sup>), 2.93 (s, 2H, H<sup>1</sup>), 0.40 (s, 6H, H<sup>2</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)** δ 161.0, 135.4, 127.0, 113.9, 55.2, 30.9, -4.2.

**HRMS (ESI)** m/z: [M + Na]<sup>+</sup> Calcd for C<sub>10</sub>H<sub>15</sub>ClOSiNa 237.0478; Found 237.0477.

(chloromethyl)(3-methoxyphenyl)dimethylsilane (**282**)



Chemical Formula: C<sub>10</sub>H<sub>15</sub>ClOSi  
Molecular Weight: 214,76

Quantity: 880 mg

Aspect: yellow oil

Purification: not required

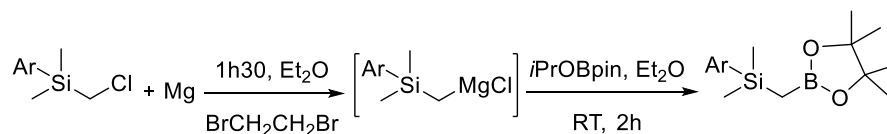
Isolated yield: quant.

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.33 (dd,  $J$  = 8.2, 7.2 Hz, 1H,  $\text{H}^4$ ), 7.12 (dt,  $J$  = 7.1, 1.0 Hz, 1H,  $\text{H}^5$ ), 7.08 (dd,  $J$  = 2.8, 0.9 Hz, 1H,  $\text{H}^6$ ), 6.95 (ddd,  $J$  = 8.2, 2.7, 0.9 Hz, 1H,  $\text{H}^3$ ), 3.83 (s, 3H,  $\text{H}^7$ ), 2.95 (s, 2H,  $\text{H}^1$ ), 0.42 (s, 6H,  $\text{H}^2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ )**  $\delta$  159.2, 137.9, 129.4, 126.1, 119.6, 114.9, 55.3, 30.5, -4.4.

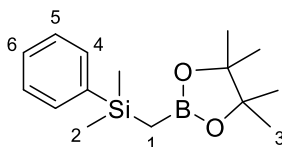
**HRMS (ESI)**  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{10}\text{H}_{15}\text{ClOSiNa}$  237.0478; Found 237.0488.

General procedure the borylation of  $\alpha$ -chlorosilane (285, 287-288)



In a dry round-bottom flask equipped with a condenser, under inert atmosphere, magnesium turnings (48 mg, 1.97 mmol, 1.5 eq.) are placed in 3 ml of dry diethyl ether. A drop of 1,2-dibromoethane is added to activate the magnesium. The (chloromethyl)dimethylarylsilane (0.26 ml, 1.44 mmol, 1.1 eq.), as a solution in 2 ml of dry diethyl ether, is added by portions under reflux. Once the solution turns turbid, it is stirred for an additional 1h30 at RT. In a second dried flask, the *i*PrOBpin (0.27 ml, 1.32 mmol, 1.0 eq.) is dissolved in 1 ml of dry diethyl ether. The prepared Grignard is added slowly to this solution at  $-78^\circ\text{C}$ . The reaction is stirred for 2h at RT. The reaction mixture is cooled down to  $0^\circ\text{C}$  and the reaction is quenched by the addition of saturated  $\text{NH}_4\text{Cl}$  solution. The layers are separated and the aqueous one is extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

Dimethyl(phenyl)((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane (**285**)



Chemical Formula: C<sub>15</sub>H<sub>25</sub>BO<sub>2</sub>Si  
Molecular Weight: 276.26

Quantity: 112 mg

Aspect: colorless oil

Purification: flash chromatography on alumina (from 98:2 to 95:5 *n*-hexane/AcOEt)

Isolated yield: 31%

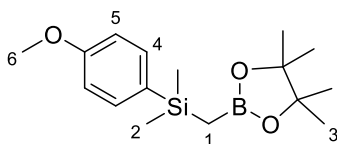
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.59-7.51 (m, 2H, H<sup>5</sup>), 7.36 – 7.30 (m, 3H, H<sup>6</sup> and <sup>4</sup>), 1.18 (s, 12H, H<sup>3</sup>), 0.36 (s, 2H, H<sup>1</sup>), 0.33 (s, 6H, H<sup>2</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)** δ 140.3, 133.6, 128.9, 127.8, 83.0, 25.0, -0.8.  
The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**<sup>11</sup>B NMR (193 MHz, CDCl<sub>3</sub>)** δ 32.67.

**HRMS (ESI)** *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>25</sub>O<sub>2</sub>BSiNa 299.1615; Found 299.1625.

(4-Methoxyphenyl)dimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane (**287**)



Chemical Formula: C<sub>16</sub>H<sub>27</sub>BO<sub>3</sub>Si  
Molecular Weight: 306.28

Quantity: 293 mg

Aspect: colorless oil

Purification: not required

Isolated yield: 81%

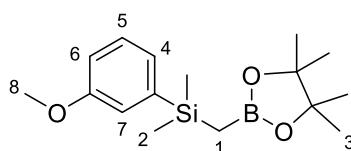
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.52 – 7.43 (m, 2H, H<sup>4</sup>), 6.95 – 6.84 (m, 2H, H<sup>5</sup>), 3.81 (s, 3H, H<sup>6</sup>), 1.19 (s, 12H, H<sup>3</sup>), 0.34 (s, 2H, H<sup>1</sup>), 0.31 (s, 9H, H<sup>2</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)** δ 160.4, 135.0, 131.2, 113.6, 82.9, 55.2, 25.0, -0.5. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**<sup>11</sup>B NMR (193 MHz, CDCl<sub>3</sub>)** δ 32.64.

**HRMS (ESI)** m/z: [M + Na]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>27</sub>O<sub>3</sub>BSiNa 329.1720; Found 329.1721.

(3-Methoxyphenyl)dimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane (**288**)



Chemical Formula: C<sub>16</sub>H<sub>27</sub>BO<sub>3</sub>Si

Molecular Weight: 306.28

Quantity: 121 mg

Aspect: colorless oil

Purification: flash chromatography on alumina (from 98:2 to 95:5 *n*-hexane/AcOEt)

Isolated yield: 34%

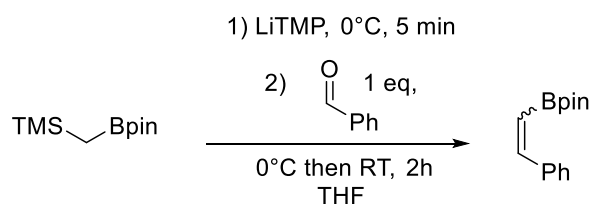
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** δ 7.28 (dd, *J* = 8.2, 7.2 Hz, 1H, H<sup>5</sup>), 7.13 (dt, *J* = 7.2, 1.0 Hz, 1H, H<sup>4</sup>), 7.10 (dd, *J* = 2.7, 0.9 Hz, 1H, H<sup>7</sup>), 6.88 (ddd, *J* = 8.2, 2.8, 1.0 Hz, 1H, H<sup>6</sup>), 3.82 (s, 3H, H<sup>8</sup>), 1.19 (s, 12H, H<sup>3</sup>), 0.36 (s, 2H, H<sup>1</sup>), 0.32 (s, 6H, H<sup>2</sup>).

**<sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)** δ 159.0, 142.0, 129.0, 125.9, 118.9, 114.3, 83.0, 55.2, 25.0, -0.8. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**<sup>11</sup>B NMR (193 MHz, CDCl<sub>3</sub>)** δ 32.70.

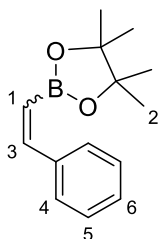
**HRMS (ESI)** *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>27</sub>O<sub>3</sub>BSiNa 329.1720; Found 329.1721.

General olefination procedure (222, 234-249)



In a dry round-bottom flask, under inert atmosphere, tetramethylpiperidine (0.16 ml, 0.94 mmol, 2.2 eq.) is dissolved in 3 ml of anhydrous THF. The solution is cooled down to 0°C. The *n*-butyl lithium (0.37 ml, 2.5 M, 0.93 mmol, 2.2 eq.) is added dropwise and the reaction is stirred for 10 minutes at 0°C. The borylsilylalkane (175 mg, 0.85 mmol, 2.0 eq.) is slowly added. The reaction is stirred for 5 additional minutes at 0°C. The aldehyde or the ketone (0.04 ml, 0.42 mmol, 1.0 eq.) is then added, as a solution in 1 ml of dry THF. The reaction mixture is warmed up to RT and the reaction is stirred 2h at RT. The mixture is filtered through a silica plug with diethyl ether, then concentrated under reduced pressure to yield vinylboronates **222**, **234-249**.

4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane (**222**)



Chemical Formula:  $C_{14}H_{19}BO_2$   
Molecular Weight: 230.11

Quantity: 204 mg (0.4 mmol scale), 473 mg (1.0 mmol scale)

Aspect: brown solid

Crude NMR yield: 56% (0.4 mmol scale), 52% (1.0 mmol scale)

Purification: flash chromatography (95:5 *n*-hexane/AcOEt)

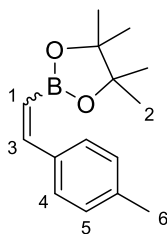
Isolated yield: 49% (0.4 mmol scale)

*Z/E* ratio: 2:1

**$^1H$  NMR (300 MHz,  $CDCl_3$ )**  $\delta$  7.58–7.27 (m, 12H,  $H^{arom}$ ,  $^3_Z$  and  $E$ ), 6.17 (d,  $J$  = 18.4 Hz, 1H,  $H^1_E$ ), 5.59 (d,  $J$  = 14.9 Hz, 1H,  $H^1_Z$ ), 1.32 (s, 12H,  $H^2_E$ ), 1.29 (s, 12H,  $H^2_Z$ ).

The description of this compound matches the one previously reported in literature.<sup>[198]</sup>

4,4,5,5-Tetramethyl-2-(4-methylstyryl)-1,3,2-dioxaborolane (**234**)



Chemical Formula:  $C_{15}H_{21}BO_2$   
Molecular Weight: 244.14

Quantity: 65 mg

Aspect: yellow oil

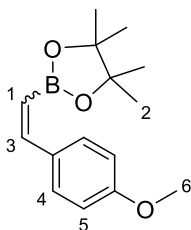
Crude NMR yield: 58%

Z/E ratio: 2:1

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.50 – 7.37 (m, 5H,  $\text{H}^4_{\text{Z and E}}$  and  $\text{H}^3_{\text{E}}$ ), 7.19 – 7.07 (m, 5H,  $\text{H}^5_{\text{Z and E}}$  and  $\text{H}^3_{\text{Z}}$ ), 6.11 (d,  $J = 18.5$  Hz, 1H,  $\text{H}^1_{\text{E}}$ ), 5.52 (d,  $J = 14.9$  Hz, 1H,  $\text{H}^1_{\text{Z}}$ ), 2.34 (s, 6H,  $\text{H}^6_{\text{Z and E}}$ ), 1.31 (s, 12H,  $\text{H}^2_{\text{E}}$ ), 1.30 (s, 12H,  $\text{H}^2_{\text{Z}}$ ).

The description of this compound matches the one previously reported in literature.<sup>[198]</sup>

#### 2-(4-Methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (235)



Chemical Formula:  $\text{C}_{15}\text{H}_{21}\text{BO}_3$   
Molecular Weight: 260.14

Quantity: 103 mg

Aspect: yellow oil

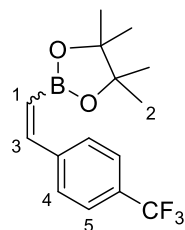
Crude NMR yield: 63%

Z/E ratio: 2:1

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.60 – 7.49 (m, 2H,  $\text{H}^4_{\text{Z}}$ ), 7.49 – 7.39 (m, 2H,  $\text{H}^4_{\text{E}}$ ), 7.35 (d,  $J = 18.4$  Hz, 1H,  $\text{H}^3_{\text{E}}$ ), 7.15 (d,  $J = 15.0$  Hz, 1H,  $\text{H}^3_{\text{Z}}$ ), 6.89 – 6.79 (m, 4H,  $\text{H}^5_{\text{Z and E}}$ ), 6.01 (d,  $J = 18.5$  Hz, 1H,  $\text{H}^1_{\text{E}}$ ), 5.45 (d,  $J = 14.9$  Hz, 1H,  $\text{H}^1_{\text{Z}}$ ), 3.82 (s, 3H,  $\text{H}^6_{\text{E}}$ ), 3.82 (s, 3H,  $\text{H}^6_{\text{Z}}$ ), 1.31 (s, 12H,  $\text{H}^2_{\text{E}}$ ), 1.30 (s, 12H,  $\text{H}^2_{\text{Z}}$ ).

The description of this compound matches the one previously reported in literature.<sup>[198]</sup>

4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)styryl)-1,3,2-dioxaborolane  
(236)



Chemical Formula:  $C_{15}H_{18}BF_3O_2$   
Molecular Weight: 298.11

Quantity: 123 mg

Aspect: yellow oil

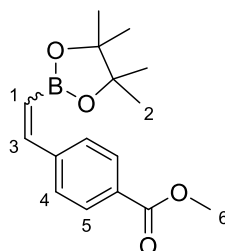
Crude NMR yield: 61%

Z/E ratio: 2:1

**$^1H$  NMR (300 MHz,  $CDCl_3$ )**  $\delta$  7.70 – 7.46 (m, 8H,  $H^4_{Z \text{ and } E}$  and  $H^5_{Z \text{ and } E}$ ), 7.40 (d,  $J = 18.4$  Hz, 1H,  $H^3_E$ ), 7.22 (d,  $J = 14.9$  Hz, 1H,  $H^3_Z$ ), 6.26 (d,  $J = 18.4$  Hz, 1H,  $H^1_E$ ), 5.73 (d,  $J = 14.9$  Hz, 1H,  $H^1_Z$ ), 1.32 (s, 12H,  $H^2_E$ ), 1.29 (s, 12H,  $H^2_Z$ ).

The description of this compound matches the one previously reported in literature.<sup>[198]</sup>

Methyl 4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzoate (238)



Chemical Formula:  $C_{16}H_{21}BO_4$   
Molecular Weight: 288.15



Quantity: 131 mg

Aspect: orange oil

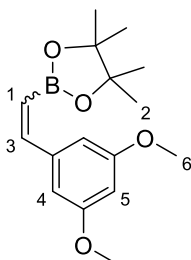
Crude NMR yield: 1%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 8.01-7.98 (m, 2H, H<sup>5</sup><sub>Z</sub>), 7.55-7.50 (m, 2H, H<sup>4</sup><sub>Z</sub>), 7.40 (d, J = 18.4 Hz, 1H, H<sup>3</sup><sub>Z</sub>), 6.27 (d, J = 18.4, 1H, H<sup>3</sup><sub>Z</sub>), 3.90 (s, 3H, H<sup>6</sup><sub>Z</sub>), 1.31 (s, 12H, H<sup>2</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[198]</sup>

The E isomer is observed at 5.72 (d, J = 14.9 Hz, 2H, H<sup>1</sup><sub>E</sub>), but other signals are too weak to be identified.

2-(3,5-Dimethoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**239**)



Chemical Formula: C<sub>16</sub>H<sub>23</sub>BO<sub>4</sub>

Molecular Weight: 290.17

Quantity: 104 mg

Aspect: brown oil

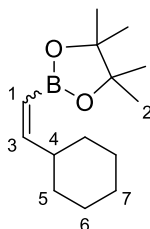
Crude NMR yield: 30%

Z/E ratio: 2:1

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** 7.32 (d, *J* = 18.4 Hz, 1H, H<sup>3</sup><sub>E</sub>), 7.12 (d, *J* = 15.0 Hz, 1H, H<sup>3</sup><sub>Z</sub>), 6.85 (d, *J* = 2.3 Hz, 2H, H<sup>4</sup><sub>Z</sub>), 6.65 (d, *J* = 2.3 Hz, 2H, H<sup>4</sup><sub>E</sub>), 6.42 (t, *J* = 2.3 Hz, 1H, H<sup>5</sup><sub>E</sub>), 6.40 (t, *J* = 2.3 Hz, 1H, H<sup>5</sup><sub>Z</sub>), 6.14 (d, *J* = 18.4 Hz, 1H, H<sup>1</sup><sub>E</sub>), 5.58 (d, *J* = 15.0 Hz, 1H, H<sup>1</sup><sub>Z</sub>), 3.80 (s, 6H, H<sup>6</sup><sub>Z</sub>), 3.79 (s, 6H, H<sup>6</sup><sub>E</sub>), 1.31 (s, 12H, H<sup>2</sup><sub>E</sub>), 1.29 (s, 12H, H<sup>2</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[204]</sup>

#### 2-(2-Cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**240**)



Chemical Formula: C<sub>14</sub>H<sub>25</sub>BO<sub>2</sub>  
Molecular Weight: 236.16

Quantity: 88 mg

Aspect: yellow oil

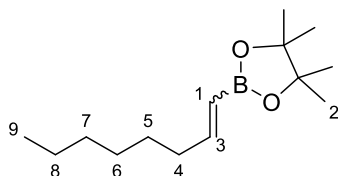
Crude NMR yield: 63%

*Z/E* ratio: 3:2

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** δ 6.58 (dd, *J* = 18.2, 6.2 Hz, 1H, H<sup>3</sup><sub>E</sub>), 6.25 (dd, *J* = 13.5, 9.3 Hz, 1H, H<sup>3</sup><sub>Z</sub>), 5.37 (dd, *J* = 18.2, 1.5 Hz, 1H, H<sup>1</sup><sub>E</sub>), 5.22 (dd, *J* = 13.5, 0.8 Hz, 1H, H<sup>1</sup><sub>Z</sub>), 2.76 – 2.64 (m, 1H, H<sup>4</sup><sub>Z</sub>), 2.02 (m, 1H, H<sup>4</sup><sub>E</sub>), 1.79 – 1.65 (m, 6H, H<sup>5</sup> and <sup>7</sup><sub>Z</sub>), 1.67 – 1.61 (m, 6H, H<sup>5</sup> and <sup>7</sup><sub>E</sub>), 1.23 – 1.08 (m, 4H, H<sup>6</sup><sub>E</sub>), 1.14 – 1.02 (m, 4H, H<sup>6</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[86b]</sup>

4,4,5,5-Tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane (**241**)



Chemical Formula:  $C_{14}H_{27}BO_2$   
Molecular Weight: 238.18

Quantity: 99 mg

Aspect: orange oil

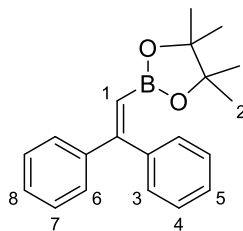
Crude NMR yield: 49%

Z/E ratio: 3:2

**$^1H$  NMR (600 MHz,  $CDCl_3$ )** 6.63 (dt,  $J = 18.0, 6.4$  Hz, 1H,  $H^3_E$ ), 6.43 (dt,  $J = 13.6, 7.5$  Hz, 1H,  $H^3_Z$ ), 5.42 (dt,  $J = 17.9, 1.6$  Hz, 1H,  $H^1_E$ ), 5.32 (dt,  $J = 13.5, 1.4$  Hz, 1H,  $H^1_Z$ ), 2.38 (m, 2H,  $H^4_Z$ ), 2.14 (m, 2H,  $H^4_E$ ), 1.46 – 1.24 (m, 16H,  $H^{5-Z \text{ and } E}$ ), 1.26 (s, 12H,  $H^2_Z$ ), 1.26 (s, 12H,  $H^2_E$ ), 0.88 (t,  $J = 7.1$  Hz, 3H,  $H^9_Z$ ), 0.87 (t,  $J = 6.9$  Hz, 3H,  $H^9_E$ ).

The description of this compound matches the one previously reported in literature.<sup>[205]</sup>

2-(2,2-Diphenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**242**)



Chemical Formula:  $C_{20}H_{23}BO_2$   
Molecular Weight: 306.21

Quantity: 120 mg

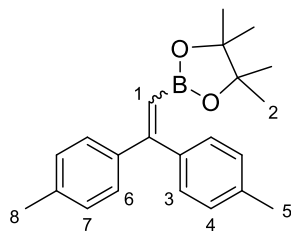
Aspect: yellow oil

Crude NMR yield: 68%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.36 – 7.20 (m, 10H, H<sup>arom</sup>), 5.99 (s, 1H, H<sup>1</sup>), 1.15 (s, 12H, H<sup>2</sup>).

The description of this compound matches the one previously reported in literature.<sup>[206]</sup>

2-(2,2-Di-*p*-tolylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**243**)



Chemical Formula: C<sub>22</sub>H<sub>27</sub>BO<sub>2</sub>  
Molecular Weight: 334.27

Quantity: 367 mg

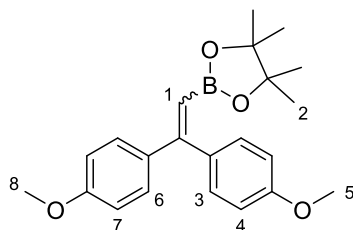
Aspect: yellow oil

Crude NMR yield: 63%

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.24 – 7.04 (m, 8H, H<sup>arom</sup>), 5.88 (s, 1H, H<sup>1</sup>), 2.37 (s, 3H, H<sup>5 or 8</sup>), 2.33 (s, 3H, H<sup>8 or 5</sup>), 1.16 (s, 12H, H<sup>2</sup>).

The description of this compound matches the one previously reported in literature.<sup>[207]</sup>

2-(2,2-Bis(4-methoxyphenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**244**)



Chemical Formula:  $C_{22}H_{27}BO_4$   
Molecular Weight: 366.26

Quantity: 237 mg

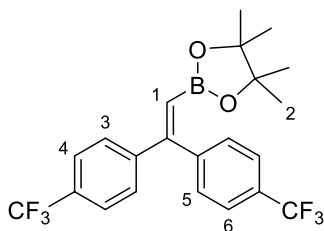
Aspect: yellow solid

Crude NMR yield: 65%

**$^1H$  NMR (300 MHz,  $CDCl_3$ )**  $\delta$  7.27 – 7.14 (m, 4H,  $H^3$  or  $4$ ), 6.88 – 6.76 (m, 4H,  $H^4$  or  $3$ ), 5.80 (s, 1H,  $H^1$ ), 3.84 (s, 3H,  $H^5$  or  $8$ ), 3.80 (s, 3H,  $H^8$  or  $5$ ), 1.17 (s, 12H,  $H^2$ ).

The description of this compound matches the one previously reported in literature.<sup>[207]</sup>

2-(2,2-Bis(4-(trifluoromethyl)phenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**245**)



Chemical Formula:  $C_{22}H_{21}BF_6O_2$   
Molecular Weight: 442.21

Quantity: 417 mg

Aspect: yellow oil

Crude NMR yield: 35%

Purification: flash chromatography (from 98:2 to 95:5 *n*-hexane/AcOEt)

Isolated yield: 2%

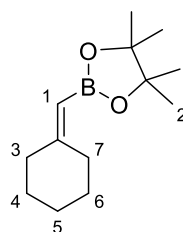
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.63 – 7.53 (m, 4H,  $\text{H}^{4 \text{ and } 6}$ ), 7.41 – 7.33 (m, 4H,  $\text{H}^{3 \text{ and } 5}$ ), 6.15 (s, 1H,  $\text{H}^1$ ), 1.14 (s, 12H,  $\text{H}^2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  157.3, 145.7, 144.8, 130.2, 128.2, 125.4 (q,  $J = 3.9$  Hz), 124.9 (q,  $J = 4.0$  Hz), 83.7, 29.9, 24.7.

**$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )**  $\delta$  30.72.

**HRMS (ESI)**  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{22}\text{O}_2\text{BF}_6$  443.16170; Found 443.16174.

2-(Cyclohexylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane  
(246)



Chemical Formula:  $\text{C}_{13}\text{H}_{23}\text{BO}_2$

Molecular Weight: 222.14

Quantity: 82 mg

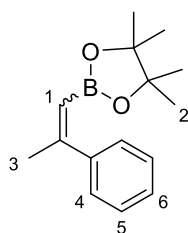
Aspect: yellow oil

Crude NMR yield: 52%

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  5.01 (s, 12H,  $\text{H}^1$ ), 2.53 – 2.48 (m, 2H,  $\text{H}^7$ ), 2.21 – 2.17 (m, 2H,  $\text{H}^3$ ), 1.63 – 1.50 (m, 6H,  $\text{H}^{4-6}$ ), 1.25 (s, 12H,  $\text{H}^2$ ).

The description of this compound matches the one previously reported in literature.<sup>[208]</sup>

4,4,5,5-Tetramethyl-2-(2-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane  
(247)



Chemical Formula: C<sub>15</sub>H<sub>21</sub>BO<sub>2</sub>  
Molecular Weight: 244.14

Quantity: 117 mg

Aspect: yellow oil

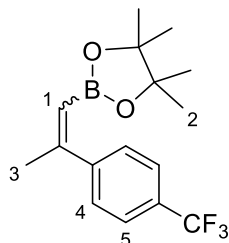
Crude NMR yield: 48%

Z/E ratio: 7:1

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** δ 7.54 – 7.46 (m, 2H, H<sup>5</sup><sub>E</sub>), 7.36 – 7.33 (m, 2H, H<sup>4</sup><sub>E</sub>), 7.32 – 7.26 (m, 6H, H<sup>4-5</sup><sub>Z</sub> and H<sup>6</sup><sub>Z and E</sub>), 5.76 (q, *J* = 1.0 Hz, 1H, H<sup>1</sup><sub>E</sub>), 5.47 (q, *J* = 1.4 Hz, 1H, H<sup>1</sup><sub>Z</sub>), 2.41 (d, *J* = 0.9 Hz, 3H, H<sup>3</sup><sub>E</sub>), 2.21 (d, *J* = 1.4 Hz, 3H, H<sup>3</sup><sub>Z</sub>), 1.32 (s, 12H, H<sup>2</sup><sub>E</sub>), 1.15 (s, 12H, H<sup>2</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[209]</sup>

4,4,5,5-tetramethyl-2-(2-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-  
1,3,2-dioxaborolane (**248**)



Chemical Formula: C<sub>16</sub>H<sub>20</sub>BF<sub>3</sub>O<sub>2</sub>  
Molecular Weight: 312.14

Quantity: 134 mg

Aspect: yellow oil

Crude NMR yield: 39%

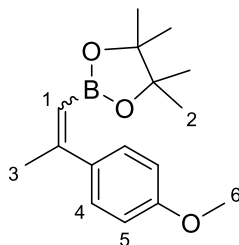
Z/E ratio: 2:1

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** 8.06 (d, *J* = 7.9 Hz, 2H, H<sup>4</sup><sub>Z</sub>), 7.73 (d, *J* = 8.0 Hz, 2H, H<sup>5</sup><sub>Z</sub>), 7.53 (d, *J* = 7.7 Hz, 2H, H<sup>4</sup><sub>E</sub>), 7.38 (d, *J* = 7.9 Hz, 2H, H<sup>5</sup><sub>E</sub>), 5.78 (q, *J* = 1.1 Hz, 1H, H<sup>1</sup><sub>E</sub>), 5.55 (q, *J* = 1.4 Hz, 1H, H<sup>1</sup><sub>Z</sub>), 2.40 (d, *J* = 1.0 Hz, 3H, H<sup>3</sup><sub>E</sub>), 2.20 (d, *J* = 1.4 Hz, 3H, H<sup>3</sup><sub>Z</sub>), 1.31 (s, H<sup>12</sup><sub>E</sub>), 1.12 (s, 12H, H<sup>2</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[209]</sup>



2-(2-(4-methoxyphenyl)prop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**249**)



Chemical Formula: C<sub>16</sub>H<sub>23</sub>BO<sub>3</sub>  
Molecular Weight: 274.17

Quantity: 122 mg

Aspect: yellow oil

Crude NMR yield: 50%

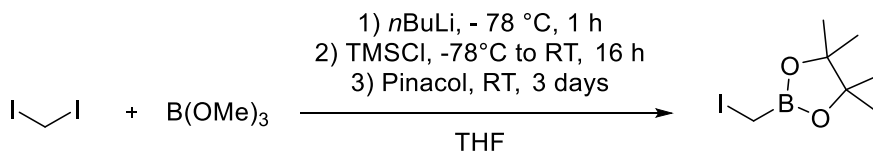
Z/E ratio: 2:1

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)** δ 7.51 – 7.43 (m, 2H, H<sup>4</sup><sub>E</sub>), 7.28 – 7.26 (m, 2H, H<sup>4</sup><sub>Z</sub>), 6.89 – 6.81 (m, 2H, H<sup>5</sup><sub>E</sub>), 6.86 – 6.77 (m, 2H, H<sup>5</sup><sub>Z</sub>), 5.70 (q, *J* = 0.9 Hz, 1H, H<sup>1</sup><sub>E</sub>), 5.39 (q, *J* = 1.3 Hz, 1H, H<sup>1</sup><sub>Z</sub>), 3.81 (s, 3H, H<sup>6</sup><sub>Z</sub>), 3.81 (s, 3H, H<sup>6</sup><sub>E</sub>), 2.39 (d, *J* = 0.9 Hz, 3H, H<sup>3</sup><sub>E</sub>), 2.19 (d, *J* = 1.4 Hz, 3H, H<sup>3</sup><sub>Z</sub>), 1.31 (s, 12H, H<sup>2</sup><sub>E</sub>), 1.17 (s, 12H, H<sup>2</sup><sub>Z</sub>).

The description of this compound matches the one previously reported in literature.<sup>[209]</sup>

2-(Iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**299**)

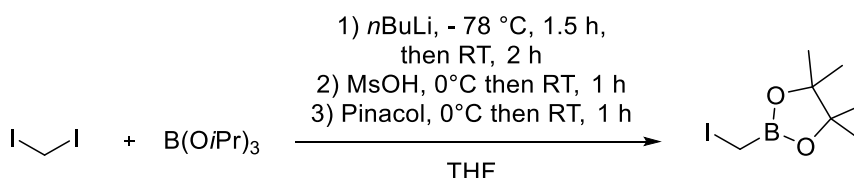
#### Protocol A:



In a dry round-bottom flask under inert atmosphere, the diiodomethane (1.00 ml, 12.48 mmol, 1.0 eq.) and trimethoxyborate (1.40 ml, 12.61 mmol, 1.0 eq.) are dissolved in 15 ml of dry THF. The solution is

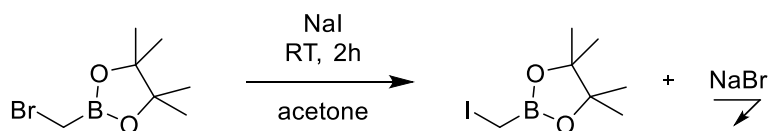
cooled to  $-78^{\circ}\text{C}$ , and the *n*buthyllithium (5.00 ml, 2.5 M, 12.54 mmol, 1.0 eq.) is added dropwise. The reaction is stirred one hour at  $-78^{\circ}\text{C}$ , then the trimethylilylchloride (1.60 ml, 12.64 mmol, 1.0 eq.) is added, and the mixture is allowed to return to RT overnight. A solution of pinacol (1.480 g, 12.50 mmol, 1.0 eq.) in 2.5 ml of THF is added and the reaction is stirred for three more days. Distilled water is added to quench the reaction, and the layers are separated. The aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product is purified by distillation under reduced pressure at  $110^{\circ}\text{C}$  (in the absence of light), to yield **299** (1.127 g, 34%) as a yellow oil.

**Protocol B:**

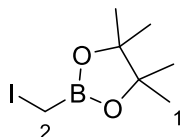


In a dry round-bottom flask under inert atmosphere, the diiodomethane (0.27 ml, 3.30 mmol, 1.2 eq.) and triisopropoxyborate (0.7 ml, 3.03 mmol, 1.1 eq.) are dissolved in 4 ml of dry THF. The solution is cooled to  $-78^{\circ}\text{C}$ , and the *n*buthyllithium (1.10 ml, 2.5 M, 2.75 mmol, 1.0 eq.) is added dropwise. The reaction is stirred one and a half hour at  $-78^{\circ}\text{C}$ , then two hours at RT, and the methanesulfonic acid (0.18 ml, 2.77 mmol, 1.0 eq.) is added at  $0^{\circ}\text{C}$ . The reaction is stirred one hour at RT, a solution of pinacol (325 mg, 2.74 mmol, 1.0 eq.) in 0.5 ml of THF is added. Once more, the reaction is stirred for one hour at RT, before distilled water is added to quench the reaction. The layers are separated, and the aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to yield **299** (0.945 g, 92% NMR yield) as a brown oil that would require a purification.

**Protocol C:**



In a dry round-bottom flask, the  $\alpha$ -bromopinacolboronate **301** (989 mg, 4.51 mmol, 1.0 eq.) and sodium iodide (1.073 g, 7.21 mmol, 1.6 eq.) are dissolved in 8.4 ml of acetone. The reaction is stirred two hours at RT, then the mixture is filtered. The filtrate is concentrated under reduced pressure to yield **299** (1.075 g, 90%) as a yellow oil.



Chemical Formula:  $C_7H_{14}BIO_2$

Molecular Weight: 267.90

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  2.17 (s, 2H,  $H^2$ ), 1.27 (s, 12H,  $H^1$ ).

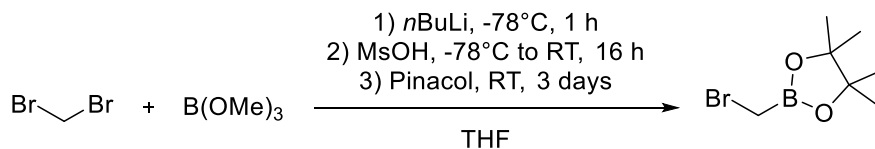
$^{13}C\{^1H\}$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  84.4, 24.6. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

$^{11}B$  NMR (160 MHz,  $CDCl_3$ )  $\delta$  32.1.

HRMS (APCI)  $m/z$ :  $[M - H]^-$  Calcd for  $C_7H_{13}BIO_2$  266.0053; Found 266.0051.

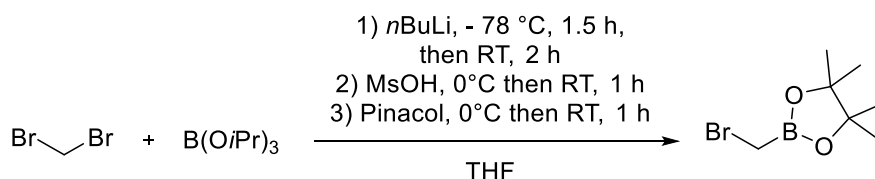
2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**301**)

**Protocol A:**

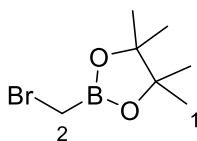


In a dry round-bottom flask under inert atmosphere, the dibromomethane (0.87 ml, 12.52 mmol, 1.0 eq.) and trimethoxyborate (1.40 ml, 12.61 mmol, 1.0 eq.) are dissolved in 15 ml of dry THF. The solution is cooled to  $-78^{\circ}\text{C}$ , and the *n*buthyllithium (5.00 ml, 2.5 M, 12.54 mmol, 1.0 eq.) is added dropwise. The reaction is stirred one hour at  $-78^{\circ}\text{C}$ , then the methanesulfonic acid (0.81 ml, 12.64 mmol, 1.0 eq.) is added, and the mixture is allowed to return to RT overnight. A solution of pinacol (1.477 g, 12.50 mmol, 1.0 eq.) in 2.5 ml of THF is added and the reaction is stirred for three more days. Distilled water is added to quench the reaction, and the layers are separated. The aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product is purified by distillation under reduced pressure at  $80^{\circ}\text{C}$ , to yield **301** (1.339 g, 49%) as a colourless oil.

**Protocol B:**



In a dry round-bottom flask under inert atmosphere, the dibromomethane (0.23 ml, 3.32 mmol, 1.2 eq.) and triisopropoxyborate (0.70 ml, 3.03 mmol, 1.1 eq.) are dissolved in 4 ml of dry THF. The solution is cooled to  $-78^{\circ}\text{C}$ , and the *n*buthyllithium (1.10 ml, 2.5 M, 2.75 mmol, 1.0 eq.) is added dropwise. The reaction is stirred one and a half hour at  $-78^{\circ}\text{C}$ , then two hours at RT, and the methanesulfonic acid (0.18 ml, 2.77 mmol, 1.0 eq.) is added at  $0^{\circ}\text{C}$ . The reaction is stirred one hour at RT, a solution of pinacol (325 mg, 2.74 mmol, 1.0 eq.) in 0.5 ml of THF is added. Once more, the reaction is stirred for one hour at RT, before distilled water is added to quench the reaction. The layers are separated, and the aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to yield **301** (0.484 g, 56% NMR yield) as a light-yellow oil that would require a purification.



Chemical Formula:  $C_7H_{14}BBrO_2$

Molecular Weight: 220.90

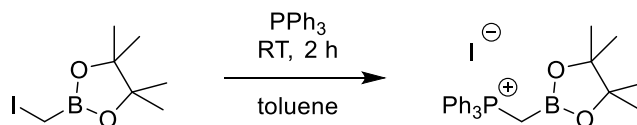
$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  2.59 (s, 2H,  $H^2$ ), 1.29 (s, 12H,  $H^1$ ).

$^{13}C\{^1H\}$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  84.7, 24.7. The signal corresponding to carbon 2 could not be observed due to quadrupolar effect.

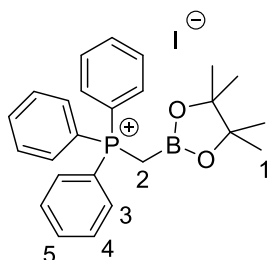
$^{11}B$  NMR (160 MHz,  $CDCl_3$ )  $\delta$  31.4.

HRMS (APCI)  $m/z$ :  $[M - H]^-$  Calcd for  $C_7H_{13}BBrO_2$  219.0192; Found 219.0190.

Triphenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phosphonium iodide (**300**)



In a dry round-bottom flask, the  $\alpha$ -iodopinacolboronate **299** (86 mg, 0.29 mmol, 1.0 eq.) and triphenylphosphine (85 mg, 0.31 mmol, 1.0 eq.) are dissolved in 5 ml of toluene. The reaction is stirred two hours at RT, then the mixture is filtered. The solid is washed with cold toluene to yield **300** (117mg, 68%) as a white solid.



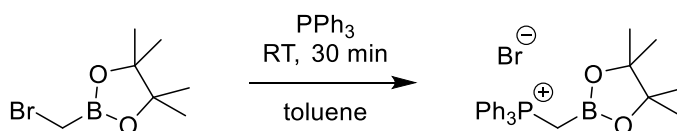
Chemical Formula:  $C_{25}H_{29}BO_2P^+I^-$   
Molecular Weight: 503.20

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.82-7.63 (m, 15H,  $H^{arom}$ ), 3.32 (d,  $J = 18.0$  Hz 2H,  $H^2$ ), 1.04 (s, 12H,  $H^1$ ).

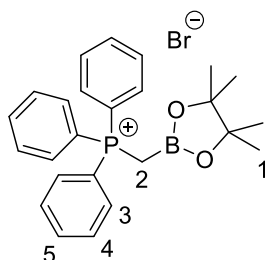
$^{11}B$  NMR (160 MHz,  $CDCl_3$ )  $\delta$  22.6.

$^{31}P$  NMR (121 MHz,  $CDCl_3$ )  $\delta$  21.8.

Triphenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phosphonium bromide (**302**)



In a dry round-bottom flask, the  $\alpha$ -bromopinacolboronate **301** (115 mg, 0.54 mmol, 1.0 eq.) and triphenylphosphine (137 mg, 0.55 mmol, 1.0 eq.) are dissolved in 5 ml of toluene. The reaction is stirred thirty minutes at RT, then the mixture is filtered. The solid is washed with cold toluene to yield **302** (101 mg, 40%) as a white solid.



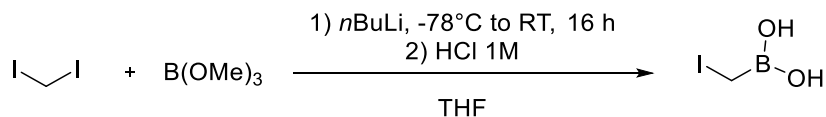
Chemical Formula:  $\text{C}_{25}\text{H}_{29}\text{BO}_2\text{P}^+\text{Br}^-$   
Molecular Weight: 483.19

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.81-7.64 (m, 15H,  $\text{H}^{\text{arom}}$ ), 3.32 (d,  $J = 18.0$  Hz 2H,  $\text{H}^2$ ), 1.05 (s, 12H,  $\text{H}^1$ ).

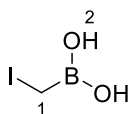
**$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )**  $\delta$  22.8.

**$^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ )**  $\delta$  21.8.

(Iodomethyl)boronic acid (**305**)



In a dry round-bottom flask under inert atmosphere, the diiodomethane (2.40 ml, 29.74 mmol, 1.0 eq.) and trimethoxyborate (3.30 ml, 29.69 mmol, 1.0 eq.) are dissolved in 36 ml of dry THF. The solution is cooled to  $-78^\circ\text{C}$ , and the *n*buthyllithium (11.9 ml, 2.5 M, 29.70 mmol, 1.0 eq.) is added dropwise. The reaction is allowed to return to RT overnight, and then quenched by HCl 1M. The layers are separated, and the aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue is washed with DCM to yield **305** (3.447 g, 45% NMR yield) as a brown oil.



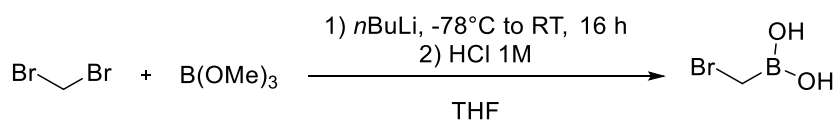
Chemical Formula:  $\text{CH}_4\text{BIO}_2$   
Molecular Weight: 185,76

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.67 (bs, 2H,  $\text{H}^1$ ), 2.31 (s, 2H,  $\text{H}^2$ ).

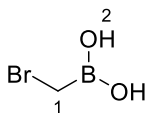
$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  no signals. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )  $\delta$  30.7.

(Bromomethyl)boronic acid (**306**)



In a dry round-bottom flask under inert atmosphere, the dibromomethane (2.20 ml, 31.55 mmol, 1.0 eq.) and trimethoxyborate (3.50 ml, 31.52 mmol, 1.0 eq.) are dissolved in 38 ml of dry THF. The solution is cooled to  $-78^\circ\text{C}$ , and the *n*buthyllithium (12.6 ml, 2.5 M, 31.57 mmol, 1.0 eq.) is added dropwise. The reaction is allowed to return to RT overnight, and then quenched by HCl 1M. The layers are separated, and the aqueous phase is extracted three times with diethyl ether, then the combined organic layers are washed with brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue is washed with DCM to yield **306** (1.542 g, 35%) as a white solid.



Chemical Formula:  $\text{CH}_4\text{BBrO}_2$   
Molecular Weight: 138,76

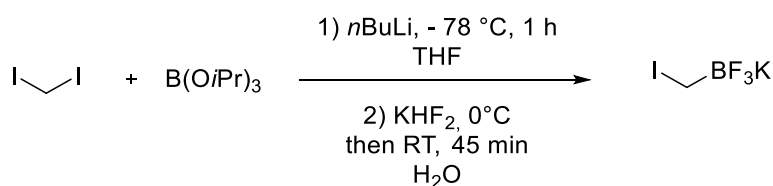
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.88 (bs, 2H,  $\text{H}^1$ ), 3.11 (s, 2H,  $\text{H}^2$ ).



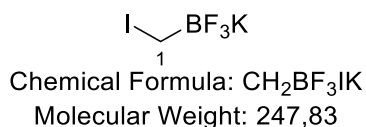
**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  no signals. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**$^{11}\text{B}$  NMR (160 MHz,  $\text{CDCl}_3$ )**  $\delta$  30.9.

Potassium (iodomethyl)trifluoroborate (**309**)



In a dry round-bottom flask under inert atmosphere, the diiodomethane (0.87 ml, 10.81 mmol, 1.2 eq.) and triisopropoxyborate (2.30 ml, 10.06 mmol, 1.1 eq.) are dissolved in 15 ml of dry THF. The solution is cooled to  $-78^\circ\text{C}$ , and the *n*buthyllithium (3.60 ml, 2.5 M, 9.00 mmol, 1.0 eq.) is added dropwise. The reaction is vigorously stirred for one hour before the temperature is raised to  $0^\circ\text{C}$ . The potassium bifluoride (2.109 g, 27.02 mmol, 3.0 eq.) and 6.4 ml of distilled water are added, in one portion and dropwise respectively. The reaction is stirred at RT for an additional 45 minutes, then the solvents are evaporated under reduced pressure. The residue is taken in a minimum of acetone, and a precipitation is triggered by the addition of diethyl ether to yield **309** (1.490 g, 67%) as a white solid.



**$^1\text{H}$  NMR (300 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  1.81 (bs, 2H,  $\text{H}^1$ ).

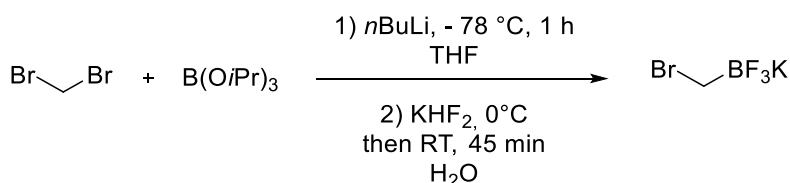
**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  no signals. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**$^{11}\text{B}$  NMR (160 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  2.87 (q,  $J = 50.1$  Hz).

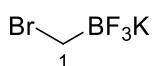
**$^{19}\text{F}$  NMR (282 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  -144.2 (q,  $J$  = 49.4 Hz)

**HRMS (ESI-)**  $m/z$ :  $[\text{M} - \text{K}]^-$  Calcd for  $\text{CH}_2\text{BIF}_3$  207,9277; Found 207,9223.

Potassium (bromomethyl)trifluoroborate (**308**)



In a dry round-bottom flask under inert atmosphere, the dibromomethane (0.75 ml, 10.77 mmol, 1.2 eq.) and triisopropoxyborate (2.30 ml, 10.06 mmol, 1.1 eq.) are dissolved in 15 ml of dry THF. The solution is cooled to  $-78^\circ\text{C}$ , and the *n*buthyllithium (3.60 ml, 2.5 M, 9.00 mmol, 1.0 eq.) is added dropwise. The reaction is vigorously stirred for one hour before the temperature is raised to  $0^\circ\text{C}$ . The potassium bifluoride (2.109 g, 27.02 mmol, 3.0 eq.) and 6.4 ml of distilled water are added, in one portion and dropwise respectively. The reaction is stirred at RT for an additional 45 minutes, then the solvents are evaporated under reduced pressure. The residue is taken in a minimum of acetone, and a precipitation is triggered by the addition of diethyl ether to yield **308** (1.155 g, 65%) as a white solid.



Chemical Formula:  $\text{CH}_2\text{BBrF}_3\text{K}$   
Molecular Weight: 200,83

**$^1\text{H}$  NMR (300 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  2.21 (bs, 2H,  $\text{H}^1$ ).

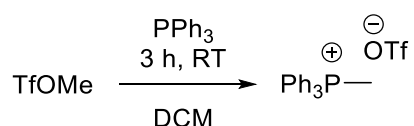
**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  no signals. The signal corresponding to carbon 1 could not be observed due to quadrupolar effect.

**$^{11}\text{B}$  NMR (160 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  2.86 (q,  $J$  = 51.1 Hz).

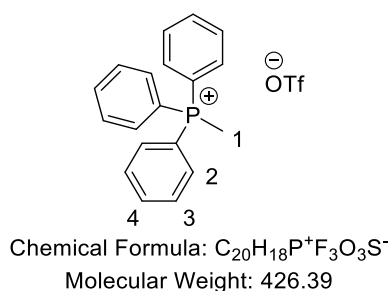
**$^{19}\text{F}$  NMR (282 MHz,  $(\text{CD}_3)_2\text{CO}$ )**  $\delta$  -145.7 (q,  $J$  = 49.5 Hz)

**HRMS (ESI-)**  $m/z$ :  $[\text{M} - \text{K}]^-$  Calcd for  $\text{CH}_2\text{BBrF}_3$  159,9416; Found 159,9368.

Tris(phenyl)methylphosphonium triflate (**314**)



In a dry round-bottom flask, the methyltriflate (0.66 ml, 5.81 mmol, 1.0 eq.) and triphenylphosphine (1.530 g, 5.86 mmol, 1.0 eq.) are dissolved in 20 ml of DCM. The reaction is stirred three hours at RT, then the mixture is concentrated under reduced pressure to yield **314** (2.487 g, quant.) as white crystals.



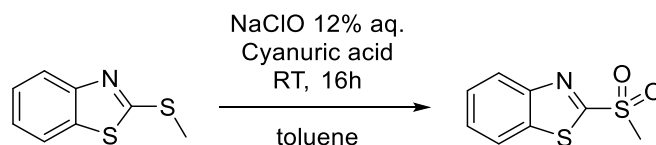
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.84-7.62 (m, 12H,  $\text{H}^{\text{arom}}$ ), 2.96 (d,  $J$  = 13.3 Hz 3H,  $\text{H}^1$ )

**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )**  $\delta$  135.4 (d,  $J$  = 3.0 Hz), 133.2 (d,  $J$  = 10.7 Hz), 130.6 (d,  $J$  = 13.0 Hz), 119.1 (d,  $J$  = 88.8 Hz), 9.6 (d,  $J$  = 58.4 Hz,)

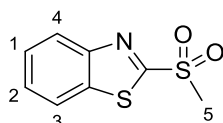
**$^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ )**  $\delta$  21.7.

**HRMS (ESI+)**  $m/z$ :  $[\text{M} - \text{OTf}]^-$  Calcd for  $\text{C}_{19}\text{H}_{18}\text{P}$  277.1141; Found 277.1123.

## 2-(methylsulfonyl)benzo[d]thiazole (**321**)



In a dry round-bottom flask, the thioether (3.000 g, 16.53 mmol, 1.0 eq.), and the cyanuric acid (214 mg, 1.65 mmol, 0.1 eq.) are dissolved in 32 ml of toluene. An aqueous solution of sodium hypochlorite (33.00 ml, 12% active chlorine, 16.49 mmol, 1.0 eq.) is then added, and the mixture is stirred at RT overnight. The reaction is diluted with 63 ml of AcOEt, sodium sulfite (2.086 g, 16.57 mmol, 1.0 eq.) is added and stirred for 30 minutes to quench the reaction. The layers are separated, and the organic phase is washed with NaOH 0.3 M. The crude mixture is concentrated under reduced pressure to yield **321** (3.295 g, 93%) as a white solid.



Chemical Formula: C<sub>8</sub>H<sub>7</sub>NO<sub>2</sub>S<sub>2</sub>  
Molecular Weight: 213,27

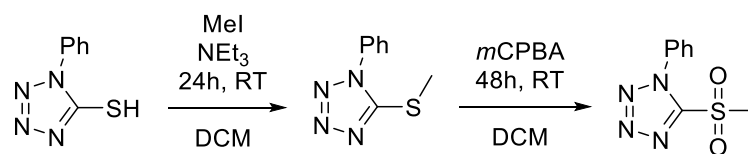
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 8.24-8.20 (m, 1H, H<sup>3</sup>), 8.04-8.01 (m, 1H, H<sup>4</sup>), 7.68-7.58 (m, 2H, H<sup>1,2</sup>), 3,42 (s, 3H, H<sup>5</sup>)

**<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)** δ 166.5, 152.6, 136.7, 128.2, 127.9, 125.6, 122.5, 42.6.

**HRMS (APCI)** m/z: [M + H]<sup>+</sup> Calcd for C<sub>8</sub>H<sub>8</sub>NO<sub>2</sub>S<sub>2</sub> 213.9991; Found 213.9990.

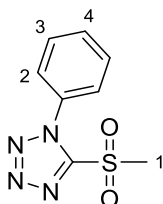
The description of this compound matches the one previously reported in literature.<sup>[197]</sup>

5-(methylsulfonyl)-1-phenyl-1*H*-tetrazole (**324**)



In a dry round-bottom flask, the thiol (1.000 g, 5.61 mmol, 1.0 eq.) is dissolved in 10 mL of DCM, and this solution is placed in a water bath (RT). The MeI (0.40 ml, 6.43 mmol, 1.2 eq.) and the triethylamine (0.89 ml, 6.39 mmol, 1.1 eq.) are added and the mixture is stirred at RT for a day. The reaction is quenched by 10 ml of HCl, then the layers are separated and the aqueous phase is extracted with three times with DCM. The combined organic phases are washed with NaHCO<sub>3</sub> and brine, dried on MgSO<sub>4</sub>, and concentrated under reduced pressure to yield 1.187 g of off-white solid. This crude is directly used in the second step of the synthesis without further analysis or purification.

The crude is dissolved in 20 mL of DCM and the *m*CPBA (3.770 g, 77% w/w, 16.82 mmol, 3.0 eq.) is added by portions. This mixture is stirred for 48 h at RT, then 10 ml of DCM are added and the reaction is quenched by 30 ml of H<sub>2</sub>O and 10ml of saturated Na<sub>2</sub>SO<sub>3</sub>. The layers are separated and the aqueous phase is extracted with three times DCM. The combined organic phases are washed 3 times with Na<sub>2</sub>CO<sub>3</sub> and brine, dried on MgSO<sub>4</sub>, and concentrated under reduced pressure to yield **324** (1.111 g, 88%) as a yellow solid.



Chemical Formula: C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>S  
Molecular Weight: 224,24

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.73 – 7.67 (m, 2H, H<sup>3</sup>), 7.66 – 7.57 (m, 3H, H<sup>2</sup> and <sup>4</sup>), 3.64 (s, 3H, H<sup>1</sup>)

**$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.0, 132.9, 131.6, 129.8, 124.9, 43.9.**

The description of this compound matches the one previously reported in literature.<sup>[213]</sup>

### 9.3. Computational study

#### 9.3.1. Methods

Calculations were performed using the Jaguar 8.5 suite of programs.<sup>[210]</sup> Density Functional Theory (DFT) was applied by the means of the B3LYP hybrid functional,<sup>[211]</sup> corrected for dispersion as proposed by Grimme (D3 correction).<sup>[212]</sup> The 6-31+G(d) basis set was used for all atoms. All the optimization calculations include an implicit description of THF solvent using the Poisson–Boltzmann polarizable continuum method as incorporated in Jaguar.

Addition TSs were optimized using the nops=1 keyword (all-analytic calculation, i.e., without the pseudo-spectral method) and the “loose” geometry convergence parameters within Jaguar. Test calculations using the standard convergence criteria led to insignificant changes in structure, but were much more time consuming.

The stationary points were characterized by full vibration frequencies calculations at the B3LYP-D3/6-31+G(d)(THF) level. Gibbs free energies at 298.15 K computed by Jaguar, which refer to an ideal gas ( $p = 1$  atm) standard state, were corrected to use a standard state corresponding to species in solution with a standard concentration of 1 M.

$$G^\circ = G^{1\text{atm}} + RT \ln(C^\circ/C^{1\text{atm}})$$

where  $G^\circ$  is the Gibbs energy with reference to the correct solution-phase standard state,  $G^{1\text{atm}}$  is the ideal gas standard Gibbs energy at 298.15 K (as output by Jaguar),  $C^\circ$  is the standard reference state concentration (1 M), and  $C^{1\text{atm}}$  is the concentration of an ideal gas under the standard  $p = 1$  atm conditions ( $C^{1\text{atm}} = 1/V_m = P/RT = 0.0409 \text{ mol l}^{-1}$ ).

We have made a systematic attempt to locate all possible local minima (at the B3LYP-D3/6-31+G(d)(THF) level), with the data presented referring to the lowest energy form.

Electronic energies were recomputed at the LCCSD/cc-pVTZ level of theory (selected after a benchmark of methods, **Table 35**) using the ORCA 5.0.3 program package.

**Table 35:** benchmark of computational methods.

| Structure                    | B3LYP-<br>D3/6-<br>31+G* | B3LYP-<br>D3/6-<br>311+G** | MO6-<br>2X/6-<br>311+G** | SCS-<br>MP2/6-<br>311+G** | LCCSD<br>/cc-<br>pVTZ |
|------------------------------|--------------------------|----------------------------|--------------------------|---------------------------|-----------------------|
| Reagents                     | 0                        | 0                          | 0                        | 0                         | 0                     |
| TSadd-RS                     | 11.6                     | 11.3                       | 11.0                     | 11.3                      | 14.5                  |
| TSadd-RR                     | 11.7                     | 11.4                       | 10.7                     | 11.1                      | 14.6                  |
| Adduct-<br>RS                | -13.2                    | -12.9                      | -24.2                    | -23.3                     | -24.4                 |
| TSelimBO<br>-RS              | 7.1                      | 9.1                        | 4.4                      | 8.3                       | 5.7                   |
| TSelimSiO<br>-RS             | 0.4                      | 0.8                        | -3.1                     | 0.1                       | 1.4                   |
| Boron-<br>Wittig<br>products | -54.0                    | -51.6                      | -58.1                    | -59.0                     | -58.5                 |
| Peterson<br>products         | -52.0                    | -54.2                      | -59.7                    | -59.8                     | -61.0                 |

*Relative free energies in kcal/mol*

### 9.3.2. Cartesian coordinates and energies

#### 9.3.2.1. Benzaldehyde

E(B3LYP-D3/6-31+G(d)(THF)) =  
-345,527084  
E(LCCSD/6-311+G(d,p)(THF)) =  
-344,297404  
G(LCCSD/6-311+G(d,p)(THF)) =  
-344,228146

C1 0.0129299687 0.0003044593  
0.2022991611  
O2 -0.7033721504 0.9981496154  
0.2221312912  
C3 1.4872535290 0.0198597541  
0.1639575988  
C4 2.2003885630 1.2340130173  
0.1469937098  
C5 3.5939838837 1.2192821977  
0.1110691237  
C6 4.2832272138 -0.0041931201  
0.0917958136  
C7 3.5784182920 -1.2142950576  
0.1083713329  
C8 2.1814640383 -1.2026888029  
0.1443038072  
H9 -0.4493954293 -1.0076853286  
0.2131941267  
H10 1.6549649359  
2.1747095905 0.1620660359  
H11 4.1475504213  
2.1560431283 0.0977544299  
H12 5.3713776929  
-0.0126224606 0.0639357287  
H13 4.1162636235  
-2.1597604729 0.0934895536  
H14 1.6256831256  
-2.1399587267 0.1570125954

#### 9.3.2.2. TMSCHBpinLi

E(B3LYP-D3/6-31+G(d)(THF)) =  
-866,625244  
E(LCCSD/6-311+G(d,p)(THF)) =  
-863,964872  
G(LCCSD/6-311+G(d,p)(THF)) =  
-863,817437

Si1 0.5215814752 0.9283857695  
3.4417406842  
C2 1.7880887171 2.2422609670  
3.2586302647  
B3 2.6226978678 2.1865057384  
2.0356983132  
O4 3.6805916630 3.0593381761  
1.5999970586  
C5 3.9706742146 2.7370635557  
0.2122295968  
C6 3.5190641407 1.2347558625  
0.1050126286  
O7 2.4375961980 1.1882537793  
1.0379754552  
C8 3.1155967856 3.6616042768  
-0.6657474905  
C9 3.0036441684 0.8095754378  
-1.2738202211  
C10 4.5957516188  
0.2398222100 0.5711910943  
C11 5.4538770910  
2.9648340927 -0.0632262271  
C12 -0.7344531180  
0.8510228321 1.9974887881  
C13 1.2386213570  
-0.8479556716 3.4657060843  
C14 -0.5255718933  
1.0888017970 5.0302195492  
H15 1.8665355476  
3.0522842946 3.9902986258  
H16 3.3212973264  
3.5145177585 -1.7325950842



H17 2.0500109294  
 3.4830616106 -0.4877467170  
 H18 3.3377688417  
 4.7043959035 -0.4117410873  
 H19 3.7766774711  
 0.9339132013 -2.0428069625  
 H20 2.7198425715  
 -0.2494042393 -1.2448114416  
 H21 2.1190079141  
 1.3817209655 -1.5662366199  
 H22 5.4265399843  
 0.1665633611 -0.1407733426  
 H23 4.9916258920  
 0.5206952179 1.5526973699  
 H24 4.1340724960  
 -0.7495904809 0.6646416773  
 H25 5.7128209232  
 2.6255803807 -1.0746146796  
 H26 5.6930306296  
 4.0328841254 0.0077294280  
 H27 6.0788232696  
 2.4234853096 0.6529473481  
 H28 -1.4036846371  
 -0.0174536410 2.0898565484  
 H29 -1.3541391732  
 1.7570060489 1.9509877648  
 H30 -0.1839145351  
 0.7665720433 1.0521824648  
 H31 0.4383642878  
 -1.6031031992 3.4495311791  
 H32 1.8667278597  
 -0.9920730868 2.5775909608  
 H33 1.8594853411  
 -1.0256361462 4.3545049265  
 H34 -1.2567166445  
 0.2694290232 5.0813689469  
 H35 0.0959142331  
 1.0397661171 5.9342925421  
 H36 -1.0827777589  
 2.0350205120 5.0517795930

Li37 4.4403601379  
 5.4092365605 3.0739755393

### 9.3.2.3. TSadd-RS

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,132437  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,295237  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,025182

Si1 1.9064828914 -0.4353744983  
 4.9718348770  
 C2 2.2448937592 1.1814105614  
 4.0454932426  
 B3 2.9129660042 1.0466558827  
 2.6646334696  
 O4 3.5924106180 -0.0823135826  
 2.2277199785  
 C5 4.3941074469 0.2513155795  
 1.0710231015  
 C6 3.7006277013 1.5703657048  
 0.5476602590  
 O7 3.0341249094 2.0853339703  
 1.7361569016  
 C8 5.8314604035 0.4575424527  
 1.5712626371  
 C9 4.6757225206 2.6286552001  
 0.0367438453  
 C10 2.6047520154  
 1.3075679318 -0.4915379372  
 C11 4.3602377100  
 -0.9263320583 0.0954423152  
 C12 0.2400010612  
 -1.1102311868 4.3374541476  
 C13 3.1576272128  
 -1.8384983390 4.6799173944  
 C14 1.7524141222  
 -0.2879130512 6.8590631552

H15 6.5219891220  
 0.6559727453 0.7438217682  
 H16 5.8946835753  
 1.2843070143 2.2863548450  
 H17 6.1574800192  
 -0.4563487412 2.0805047426  
 H18 5.2524698880  
 2.2434188496 -0.8130416574  
 H19 4.1225966676  
 3.5135692391 -0.2983530513  
 H20 5.3742780784  
 2.9390852422 0.8186106491  
 H21 3.0227627016  
 0.9545657270 -1.4407379387  
 H22 1.8874313691  
 0.5648579924 -0.1260413245  
 H23 2.0629772667  
 2.2419646249 -0.6767441284  
 H24 4.8923582703  
 -0.6783953145 -0.8311728935  
 H25 4.8533630859  
 -1.7925017506 0.5512977124  
 H26 3.3358683235  
 -1.2154337697 -0.1536968415  
 H27 -0.0009288134  
 -2.0674128785 4.8224520209  
 H28 -0.5796199538  
 -0.4092530241 4.5456968367  
 H29 0.2737680259  
 -1.2794540989 3.2528324508  
 H30 2.8194092858  
 -2.7261420165 5.2347602372  
 H31 3.2296590166  
 -2.0944704851 3.6185363907  
 H32 4.1622844302  
 -1.5833777304 5.0335063238  
 H33 1.2612534418  
 -1.1939859191 7.2426505775  
 H34 2.7385040189  
 -0.2154055775 7.3300731677

H35 1.1657456232  
 0.5823173715 7.1768703299  
 Li36 1.5326125984  
 5.2023554683 2.8676666280  
 C37 3.3158467306  
 2.6874064506 4.8103033219  
 O38 2.5435352780  
 3.7410620730 5.0431697420  
 C39 5.5602587983  
 0.6636378549 7.9443212871  
 C40 5.7705833258  
 0.3630003038 6.5902653588  
 C41 5.0494167205  
 1.0378645600 5.6067834499  
 C42 4.0905456793  
 2.0180865293 5.9354603041  
 C43 3.9070841728  
 2.3269648143 7.2890373553  
 C44 4.6322224649  
 1.6531758256 8.2847003113  
 H45 6.1129934621  
 0.1308648945 8.7167270325  
 H46 6.4878665413  
 -0.4064076899 6.3060515602  
 H47 5.1969792292  
 0.7702103135 4.5624079011  
 H48 3.1767506372  
 3.0844626099 7.5613536932  
 H49 4.4645468294  
 1.8933996809 9.3334880385  
 H50 1.3246267502  
 1.7738572018 4.0116595303  
 H51 4.0029229975  
 2.8077793589 3.9541875728

#### 9.3.2.4. TSadd-RR

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,14317

E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,348723  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,044012

C1 -0.9883199785 -0.6525912154  
 -1.7045977870  
 O2 -0.4154103997 -1.8681752926  
 -1.8548657254  
 Li3 0.5439389161 -3.3935185089  
 -1.3271891312  
 C4 -0.6372815401 0.1123494431  
 0.2193449320  
 C5 -0.5487605818 0.5182107902  
 -2.5486085231  
 C6 -1.4617880560 1.5508280643  
 -2.8506200391  
 C7 -1.0526119536 2.7143602842  
 -3.5129306212  
 C8 0.2839812819 2.8632225333  
 -3.9109405073  
 C9 1.1906067167 1.8218356441  
 -3.6606729893  
 C10 0.7774630427  
 0.6580197426 -2.9969989625  
 Si11 -1.4656192905  
 1.7552199669 0.7960667329  
 B12 0.8929394775  
 0.1920705337 0.3239601839  
 O13 1.8497189459  
 -0.6437267519 -0.2891457191  
 C14 3.2268069032  
 -0.2027155981 0.0923527824  
 C15 2.9976237357  
 1.2556431543 0.6710994585  
 O16 1.5539152708  
 1.2316202992 1.0237926422  
 C17 3.6984703574  
 -1.2143173292 1.1406013093

C18 3.7879970625  
 1.5773400034 1.9389446230  
 C19 4.0941251959  
 -0.2581464320 -1.1627769328  
 C20 3.1657234650  
 2.3787150675 -0.3622148580  
 C21 -1.3564552751  
 1.8707394257 2.7183155067  
 C22 -0.5946015925  
 3.3466975522 0.1564433169  
 C23 -3.3323100775  
 1.9543338105 0.3604536414  
 H24 -2.0835668477  
 -0.6535187820 -1.5894616799  
 H25 -1.0935840305  
 -0.7607449507 0.6995532866  
 H26 -2.4958228150  
 1.4562398426 -2.5313813349  
 H27 -1.7684386876  
 3.5104674179 -3.7050245451  
 H28 0.6114329334  
 3.7745227814 -4.4050921836  
 H29 2.2266960776  
 1.9259052063 -3.9736806630  
 H30 1.4812884515  
 -0.1313547077 -2.7665832423  
 H31 4.7213899925  
 -1.0084130010 1.4714264583  
 H32 3.0350237499  
 -1.2046552988 2.0110510836  
 H33 3.6676202925  
 -2.2146693224 0.6970976239  
 H34 4.8658505222  
 1.5468881577 1.7402800150  
 H35 3.5290498368  
 2.5847855005 2.2803543224  
 H36 3.5556453965  
 0.8776610791 2.7442919554  
 H37 5.1154893028  
 0.0719633600 -0.9406846286

H38 4.1344678409  
 -1.2860486079 -1.5367113754  
 H39 3.6870788996  
 0.3751360590 -1.9531400387  
 H40 4.2089165102  
 2.4754910720 -0.6817078315  
 H41 2.5341925396  
 2.2084469404 -1.2378661637  
 H42 2.8554057893  
 3.3234878568 0.0953079348  
 H43 -1.7531464059  
 2.8357421026 3.0620266471  
 H44 -1.9227107584  
 1.0699939002 3.2089781391  
 H45 -0.3045895276  
 1.7967177035 3.0144527606  
 H46 -1.1885706197  
 4.2221186954 0.4524478508  
 H47 0.3957362760  
 3.4162696225 0.6130616822  
 H48 -0.4807936990  
 3.3530188938 -0.9307969161  
 H49 -3.7198527138  
 2.8097531462 0.9315159039  
 H50 -3.4807684732  
 2.1694691310 -0.7027057576  
 H51 -3.9231070192  
 1.0705758951 0.6260499992  
  
*9.3.2.5. Adduct-RS*  
  
 E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,173404  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,380977  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,084451  
  
 C1 -0.0381182845 0.3837924857  
 -2.4403415473

C2 0.0154230578 0.1500378729  
 -0.8658737259  
 O3 0.4393298790 -0.6935264840  
 -3.2039338951  
 Si4 -0.6826043478 1.5448022250  
 0.2923019378  
 B5 1.4590706612 -0.0985906370  
 -0.3348786889  
 O6 1.8393898206 -1.1948268068  
 0.4207179354  
 C7 3.1745461824 -0.9518723185  
 0.9626241021  
 C8 3.7078564876 0.2205817491  
 0.0435549250  
 O9 2.4828190447 0.8195324838  
 -0.4652884997  
 C10 3.0189949008  
 -0.5622228153 2.4383635873  
 C11 4.5026928036  
 1.3004019556 0.7756930949  
 C12 3.9669012097  
 -2.2541698458 0.8719810477  
 C13 4.4825700327  
 -0.2710966087 -1.1838507948  
 C14 -0.0663197365  
 1.2994879791 2.0793663282  
 C15 -0.0593891164  
 3.2710810682 -0.1861464624  
 C16 -2.5698351501  
 1.5845508035 0.4610811802  
 H17 0.5774592962  
 1.2888866106 -2.6184875625  
 H18 -0.5965280433  
 -0.7367340766 -0.6391921320  
 H19 3.9988115099  
 -0.4536787295 2.9169788211  
 H20 2.4703441221  
 0.3717184247 2.5622194014  
 H21 2.4654898018  
 -1.3504614899 2.9607489370

H22 5.4054451981  
 0.8751360741 1.2300990857  
 H23 4.8081908293  
 2.0761739831 0.0644473145  
 H24 3.9089368887  
 1.7779771189 1.5596666759  
 H25 5.0050911895  
 -2.0958653067 1.1870380129  
 H26 3.5174154197  
 -2.9981381956 1.5394784711  
 H27 3.9624635995  
 -2.6602659875 -0.1423676480  
 H28 5.4429965193  
 -0.7163876079 -0.9035442423  
 H29 3.8969451937  
 -1.0085639762 -1.7428480614  
 H30 4.6715662192  
 0.5825719583 -1.8436902811  
 H31 -0.7085045207  
 1.8854030007 2.7525016316  
 H32 -0.0891638469  
 0.2563290848 2.4153566412  
 H33 0.9561414034  
 1.6738798681 2.2012975826  
 H34 -0.2590968621  
 3.9641802660 0.6441045883  
 H35 1.0243956126  
 3.2473515963 -0.3530673859  
 H36 -0.5420902200  
 3.6728911450 -1.0824527330  
 H37 -2.8232589050  
 2.3397187066 1.2199555324  
 H38 -3.0870502869  
 1.8429395581 -0.4658904280  
 H39 -2.9578201779  
 0.6193169885 0.8117563481  
 C40 -4.1746302708  
 1.6735475541 -2.9944403429  
 C41 -3.1209378938  
 2.5666191860 -3.2093933747

C42 -1.7948438611  
 2.1255623335 -3.1009887471  
 C43 -1.4877892485  
 0.7985530803 -2.7615602234  
 C44 -2.5596343253  
 -0.0947332252 -2.5845212987  
 C45 -3.8853172333  
 0.3346826477 -2.6945670324  
 H46 -5.2067271527  
 2.0168629793 -3.0454550777  
 H47 -3.3287062252  
 3.6109607842 -3.4390630308  
 H48 -0.9838399613  
 2.8377911090 -3.2449078442  
 H49 -2.3499197318  
 -1.1274650930 -2.3134189818  
 H50 -4.6993498292  
 -0.3654190912 -2.5123456740  
 Li51 1.7956832896  
 -1.1735493321 -4.5683027355

### 9.3.2.6. Adduct-RR

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1212,172573  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,383275  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,084621  
 C1 -0.8504915069 -0.2249095832  
 -1.6596027806  
 O2 -0.2440003507 -1.3360786092  
 -2.2591708778  
 Li3 0.4224669589 -3.1929034007  
 -2.1624616720  
 C4 -0.4238986243 -0.0171375122  
 -0.1334881656  
 C5 -0.6607220647 1.1277618078  
 -2.3821712824

|                               |                             |
|-------------------------------|-----------------------------|
| C6 -1.7572713653 1.9879798287 | H26 -2.7572867907           |
| -2.5704112831                 | 1.6410264180 -2.3158475099  |
| C7 -1.5918490020 3.2987688610 | H27 -2.4568658677           |
| -3.0365049099                 | 3.9527715895 -3.1414286573  |
| C8 -0.3129834691 3.7767404290 | H28 -0.1722971968           |
| -3.3398968142                 | 4.8038131121 -3.6737408941  |
| C9 0.7847425428 2.9171691284  | H29 1.7851426307            |
| -3.2035845931                 | 3.2776698126 -3.4382294835  |
| C10 0.6071306893              | H30 1.4686018386            |
| 1.6094224080 -2.7408592273    | 0.9628927089 -2.6180782114  |
| Si11 -1.2291440353            | H31 4.1702526822            |
| 1.3918754640 0.9169386285     | -0.2076039548 2.8410016980  |
| B12 1.1267928908              | H32 2.4118711330            |
| 0.0796668566 0.1065271963     | 0.0557353073 2.8379342123   |
| O13 1.9515333319              | H33 3.0574098040            |
| -0.9858858180 0.4223503564    | -1.5884111763 2.7058070066  |
| C14 3.2350757877              | H34 4.8206064059            |
| -0.4567522242 0.8807858634    | 1.8796776414 1.5442052477   |
| C15 3.2236627135              | H35 3.6973153963            |
| 1.0284542995 0.3366317932     | 3.0696219112 0.8536807926   |
| O16 1.8097754126              | H36 3.1994415542            |
| 1.2776975886 0.1435907156     | 2.0953873853 2.2444408291   |
| C17 3.2208117259              | H37 5.3300589684            |
| -0.5458645434 2.4115106560    | -0.9259836381 0.5766330538  |
| C18 3.7672534746              | H38 4.2692661973            |
| 2.0760144296 1.3106542358     | -2.3435137579 0.7242914105  |
| C19 4.3468557605              | H39 4.2790437132            |
| -1.3318611349 0.3108634806    | -1.4017977029 -0.7777061830 |
| C20 3.8984117749              | H40 4.9855506780            |
| 1.2035007996 -1.0295409780    | 1.0941555469 -0.9541556142  |
| C21 -0.8069307145             | H41 3.5237648198            |
| 1.0090225653 2.7338991372     | 0.4812029618 -1.7604728870  |
| C22 -0.5960252247             | H42 3.6756710444            |
| 3.1545991907 0.6140545714     | 2.2090799095 -1.4018735125  |
| C23 -3.1248893000             | H43 -1.2724553593           |
| 1.4623607352 0.8047582935     | 1.7553432691 3.3931287299   |
| H24 -1.9511757081             | H44 -1.1621098231           |
| -0.3651694364 -1.6195103239   | 0.0174676364 3.0428923095   |
| H25 -0.7562439025             | H45 0.2764399983            |
| -0.9397748126 0.3701471349    | 1.0485551922 2.9047933368   |

H46 -1.1592108130  
 3.8424924331 1.2616399973  
 H47 0.4651046199  
 3.2282387746 0.8671529831  
 H48 -0.7185224474  
 3.4826405379 -0.4219488381  
 H49 -3.4924246313  
 2.1040368764 1.6192768945  
 H50 -3.4684456723  
 1.9032529566 -0.1378559789  
 H51 -3.5932744101  
 0.4765258937 0.9148036311

### 9.3.2.7. TScycleBO-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,151717  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,324104  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,056381

C1 0.5823929209 0.5597689631  
 -2.4053535166  
 C2 0.1687344916 0.4319420865  
 -0.9085560069  
 O3 1.5791365137 -0.4404243492  
 -2.5447930832  
 Si4 0.1161525494 1.9382403434  
 0.2403252745  
 B5 1.2837978858 -0.6674814689  
 -0.5997057039  
 O6 1.0451179240 -2.0618039891  
 -0.4328007988  
 C7 1.8237598783 -2.4988892928  
 0.7090834334  
 C8 3.0056431008 -1.4594595205  
 0.7415861445  
 O9 2.3880610030 -0.2850629031  
 0.1903897734

C10 0.9193101298  
 -2.4107500421 1.9506707621  
 C11 3.5200252294  
 -1.1234416840 2.1439145892  
 C12 2.2587274138  
 -3.9460262177 0.4961037529  
 C13 4.1791021963  
 -1.8389368998 -0.1698396954  
 C14 -1.3034705471  
 3.1163125833 -0.2294036173  
 C15 -0.2326021088  
 1.3868520051 2.0271993467  
 C16 1.7150660107  
 2.9518932855 0.2577069989  
 H17 0.9905550455  
 1.5703021589 -2.6123730950  
 H18 -0.8386326820  
 -0.0040629200 -0.8310761383  
 H19 1.4190262584  
 -2.7965596711 2.8475336607  
 H20 0.6066331524  
 -1.3806823597 2.1393516917  
 H21 0.0179256862  
 -3.0092537861 1.7754931217  
 H22 3.9044482358  
 -2.0197495177 2.6469060145  
 H23 4.3331105984  
 -0.3912504577 2.0737944467  
 H24 2.7313343953  
 -0.6877505010 2.7635971296  
 H25 2.9267643063  
 -4.2697332677 1.3041636986  
 H26 1.3814334601  
 -4.6036760808 0.4966862812  
 H27 2.7788718971  
 -4.0673181417 -0.4577367752  
 H28 4.7385513841  
 -2.6970598948 0.2209333261  
 H29 3.8207299660  
 -2.0676162409 -1.1787175389

H30 4.8557089315  
 -0.9796779707 -0.2369269344  
 H31 -1.3676719537  
 3.9383003433 0.4982751875  
 H32 -1.1666271698  
 3.5570059772 -1.2245700535  
 H33 -2.2686888577  
 2.5926062668 -0.2290922910  
 H34 -0.4475660637  
 2.2610022481 2.6584271530  
 H35 -1.0962437249  
 0.7112416905 2.0839137955  
 H36 0.6325776622  
 0.8684950607 2.4560287192  
 H37 1.6225357649  
 3.7866911228 0.9673726216  
 H38 2.5532637610  
 2.3182565544 0.5665139476  
 H39 1.9459252510  
 3.3716804367 -0.7297765010  
 C40 -3.1849855062  
 0.2005780451 -4.5264314872  
 C41 -2.5969255276  
 1.4564492835 -4.3357193311  
 C42 -1.3458303030  
 1.5565115398 -3.7172268842  
 C43 -0.6648616552  
 0.4151810981 -3.2663641971  
 C44 -1.2585973638  
 -0.8384481231 -3.4731108367  
 C45 -2.5054601521  
 -0.9483714833 -4.0964506570  
 H46 -4.1636696826  
 0.1183189357 -4.9951231735  
 H47 -3.1164683155  
 2.3580217358 -4.6573408572  
 H48 -0.9061877143  
 2.5388506252 -3.5483822203  
 H49 -0.7493719806  
 -1.7184077710 -3.0851707855

H50 -2.9630101425  
 -1.9276480165 -4.2279765167  
 Li51 1.7537088116  
 -2.9909363412 -3.9977632152

### 9.3.2.8. TScycleBO-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,150933  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,310377  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,043645

C1 -0.8337953733 -0.0989599339  
 -1.4543296916  
 O2 -0.1145174592 -1.2704115137  
 -1.8008615624  
 Li3 1.7121590518 -2.5528356460  
 -3.5745611686  
 C4 -0.3566118322 0.1653315327  
 0.0087102523  
 C5 -0.6891133016 1.1161100500  
 -2.3591647143  
 C6 -1.6738961462 2.1199134143  
 -2.3159951486  
 C7 -1.5215464329 3.3143709711  
 -3.0222320892  
 C8 -0.3751108839 3.5254113202  
 -3.8002614360  
 C9 0.6001695229 2.5238639582  
 -3.8705379179  
 C10 0.4388338055  
 1.3280926825 -3.1586590380  
 Si11 0.8729216442  
 1.5058970487 0.5383567137  
 B12 0.1679775971  
 -1.3390780238 0.1443623258  
 O13 -0.6873939252  
 -2.3439878566 0.6960183995



|               |               |               |               |
|---------------|---------------|---------------|---------------|
| C14           | 0.1006096733  | H34           | 2.6686459393  |
| -3.1107709469 | 1.6372176967  | -3.9806568887 | 2.6055799189  |
| C15           | 1.5443255258  | H35           | 3.6416697896  |
| -2.9742253020 | 1.0368201226  | -2.9264061408 | 1.5546166772  |
| O16           | 1.5069039001  | H36           | 2.5916277408  |
| -1.6535873901 | 0.4627052597  | -2.2123408664 | 2.7877490610  |
| C17           | -0.0293201319 | H37           | 0.2112960276  |
| -2.4401737531 | 3.0175465986  | -5.1589775255 | 2.3426941455  |
| C18           | 2.6754606076  | H38           | -1.4384730040 |
| -3.0269510606 | 2.0630819746  | -4.5299689329 | 2.1689510887  |
| C19           | -0.4397601769 | H39           | -0.5171894037 |
| -4.5362004160 | 1.7164629077  | -4.9922108377 | 0.7260869984  |
| C20           | 1.8043056061  | H40           | 1.9204867750  |
| -3.9744822215 | -0.0983454622 | -4.9977502966 | 0.2772863415  |
| C21           | 1.2385717399  | H41           | 0.9807012981  |
| 1.2530388890  | 2.3894392259  | -3.9493599302 | -0.8195709734 |
| C22           | 2.5439432195  | H42           | 2.7288917865  |
| 1.4373276287  | -0.3531351679 | -3.6840942449 | -0.6108732468 |
| C23           | 0.1871549038  | H43           | 1.8204163773  |
| 3.2750306737  | 0.4026916397  | 2.1021628079  | 2.7754610644  |
| H24           | -1.9233233185 | H44           | 0.3178970720  |
| -0.3032466688 | -1.4069704235 | 1.1807864220  | 2.9838341813  |
| H25           | -1.2213932848 | H45           | 1.8211147157  |
| 0.3143649806  | 0.6764777316  | 0.3388318207  | 2.5499810457  |
| H26           | -2.5538764873 | H46           | 3.2773584397  |
| 1.9725366697  | -1.6895699643 | 2.0535921818  | 0.1857124199  |
| H27           | -2.2871776949 | H47           | 2.8995793398  |
| 4.0862436928  | -2.9564467016 | 0.4009451262  | -0.3724063584 |
| H28           | -0.2460642706 | H48           | 2.4758178444  |
| 4.4595162287  | -4.3439100534 | 1.8079973585  | -1.3813693269 |
| H29           | 1.4944942706  | H49           | 0.8839575924  |
| 2.6820314567  | -4.4713360450 | 3.9721749121  | 0.8901015496  |
| H30           | 1.2031304520  | H50           | 0.0507701114  |
| 0.5557015345  | -3.1802742718 | 3.5961474108  | -0.6351454442 |
| H31           | 0.4940395422  | H51           | -0.7822669465 |
| -3.0088292755 | 3.7956334269  | 3.3618550804  | 0.9123026008  |
| H32           | 0.3698209337  |               |               |
| -1.4224782468 | 3.0018829250  |               |               |
| H33           | -1.0898653432 |               |               |
| -2.3836126455 | 3.2881119304  |               |               |

### 9.3.2.9. BOcycle-trans

E(B3LYP-D3/6-31+G(d)(THF)) =

-1.212,168321

E(LCCSD/6-311+G(d,p)(THF)) =

-1208,342515

G(LCCSD/6-311+G(d,p)(THF)) =

-1208,077644

C1 -0.6200675590 0.8914840939

-1.7113000804

O2 0.6730210170 1.4921173066

-2.0002414652

C3 -0.1341902377 -0.0236091925

-0.5576882325

Si4 -0.8875594984 0.2732428506

1.1238806086

B5 1.3651372649 0.5604570378

-1.0348940107

O6 2.2431181834 1.1980670226

-0.0324554619

C7 3.4537504801 0.4342200597

0.0908710369

C8 3.1745162039 -0.8723195982

-0.7635707675

O9 2.2438371730 -0.4009940972

-1.7307020727

C10 4.5969318033

1.2703156035 -0.5003733108

C11 4.4028357687

-1.4509615048 -1.4749628536

C12 3.7351993013

0.1561121246 1.5720434010

C13 2.5289278102

-2.0126620782 0.0559672316

C14 -2.7878530261

0.1650893305 1.0390936722

C15 -0.3595798521

-1.0437222561 2.3928323538

C16 -0.3983396871

1.9811728347 1.7903224444

H17 -0.2608085884

-1.0835564504 -0.8148749500

H18 5.5711549527

0.7792809376 -0.3846082211

H19 4.4182283519

1.4575538912 -1.5640388903

H20 4.6351441337

2.2348573821 0.0200838400

H21 5.1814866723

-1.7299213611 -0.7529255488

H22 4.1110632448

-2.3559812765 -2.0222877671

H23 4.8261118763

-0.7447367780 -2.1944516053

H24 4.6022058930

-0.5075073629 1.6895894648

H25 3.9493340409

1.0937900072 2.0993500322

H26 2.8747845507

-0.3118869155 2.0571490168

H27 3.2424407855

-2.4673043337 0.7542674975

H28 1.6620324716

-1.6714182515 0.6204002525

H29 2.1877755403

-2.7867744026 -0.6412524881

H30 -3.0951123985

-0.8318434815 0.6943847719

H31 -3.2468708121

0.3394679120 2.0224520256

H32 -3.2040844841

0.8974028503 0.3347923871

H33 -0.9522660637

-0.9446845106 3.3131024288

H34 -0.5268446851

-2.0549837462 1.9974559230

H35 0.6988663396

-0.9646223403 2.6675345857

H36 -0.7359133564  
 2.7753435232 1.1102203679  
 H37 -0.8272001099  
 2.1751076952 2.7826799999  
 H38 0.6953189292  
 2.0299198014 1.8486065953  
 C39 -2.4540186875  
 -1.6105643787 -4.7378634784  
 C40 -1.0642388810  
 -1.6315029946 -4.5506526438  
 C41 -0.4632718659  
 -0.7861065095 -3.6141180422  
 C42 -1.2393934794  
 0.1001227574 -2.8463412568  
 C43 -2.6266168636  
 0.1234887412 -3.0510199876  
 C44 -3.2333532772  
 -0.7265943974 -3.9841489871  
 H45 -2.9220873652  
 -2.2783357546 -5.4589690471  
 H46 -0.4492253871  
 -2.3215168355 -5.1269845848  
 H47 0.6076011431  
 -0.8325800108 -3.4359826213  
 H48 -3.2427648661  
 0.7979954144 -2.4579511441  
 H49 -4.3134105365  
 -0.7015819324 -4.1186019125  
 H50 -1.3241588020  
 1.6840842083 -1.4105482387  
 Li51 1.8765869827  
 4.2114812258 -0.3762442567

#### 9.3.2.10. BOcycle-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1212,167164  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,332853

G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,076929

C1 -0.0866811120 1.1565526062  
 -1.7939637195  
 O2 1.2215763785 1.7725224940  
 -1.6885657160  
 C3 -0.0122608748 0.3691561318  
 -0.4564707660  
 C4 -1.2344421828 2.1116923320  
 -2.0140478469  
 C5 -2.4539413546 1.6017364794  
 -2.4921674151  
 C6 -3.5754541298 2.4221504908  
 -2.6198974114  
 C7 -3.4938922355 3.7796386435  
 -2.2797617012  
 C8 -2.2775701726 4.3014074347  
 -1.8258634626  
 C9 -1.1567953419 3.4717821178  
 -1.6987135202  
 Si10 -0.8856822338  
 0.9470022237 1.1030732401  
 B11 1.6092793061  
 0.7422896811 -0.6468070266  
 O12 2.4024413536  
 1.2374957986 0.4851243203  
 C13 3.5397279224  
 0.3881431003 0.6850881824  
 C14 3.1871035685  
 -0.9045095847 -0.1494189193  
 O15 2.4230708015  
 -0.3603302044 -1.2261261979  
 C16 4.7738274464  
 1.1127814264 0.1273032633  
 C17 4.3991407989  
 -1.6564513608 -0.7064940387  
 C18 3.7265486843  
 0.1343137651 2.1840304026

C19 2.3231477101  
 -1.9080891212 0.6445352561  
 C20 -0.5497444683  
 -0.2953703570 2.5068178489  
 C21 -0.2636285220  
 2.6293423844 1.7261749052  
 C22 -2.7832741002  
 1.0191374380 0.9628441076  
 H23 -0.0894421889  
 0.4434988551 -2.6358614132  
 H24 -0.2457761436  
 -0.6970382171 -0.5885515885  
 H25 -2.5256581314  
 0.5437632294 -2.7439503610  
 H26 -4.5142447817  
 2.0046415434 -2.9803321587  
 H27 -4.3671289052  
 4.4218726496 -2.3755938177  
 H28 -2.2014143354  
 5.3569176379 -1.5700207293  
 H29 -0.2089876915  
 3.8677075327 -1.3473949186  
 H30 5.7013639775  
 0.5578653393 0.3151349641  
 H31 4.6636192095  
 1.2680964266 -0.9506380374  
 H32 4.8547209434  
 2.0924248402 0.6135818124  
 H33 5.0671154564  
 -1.9750132747 0.1044773167  
 H34 4.0617113692  
 -2.5560429079 -1.2362581481  
 H35 4.9683369948  
 -1.0431062134 -1.4103148282  
 H36 4.5288613685  
 -0.5933730542 2.3633336451  
 H37 3.9931923940  
 1.0688553176 2.6927977042  
 H38 2.8077725497  
 -0.2444142104 2.6389734760

H39 2.9014242131  
 -2.4084590170 1.4310046570  
 H40 1.4608796547  
 -1.4239126535 1.1032797933  
 H41 1.9508057022  
 -2.6739304584 -0.0461426525  
 H42 -1.1686596420  
 -0.0439231545 3.3796911154  
 H43 -0.7967063708  
 -1.3229516250 2.2078412212  
 H44 0.4992959520  
 -0.2785199252 2.8238774472  
 H45 -0.7155547175  
 2.8721565711 2.6979340103  
 H46 0.8241515765  
 2.5654982637 1.8427279015  
 H47 -0.5048160226  
 3.4367759945 1.0256576105  
 H48 -3.2249730895  
 1.2305467923 1.9472829394  
 H49 -3.1197966218  
 1.7891874824 0.2607741634  
 H50 -3.1825353454  
 0.0561109672 0.6154080360  
 Li51 2.5645719899  
 4.5042232396 0.0604221107

### 9.3.2.11. TSelimBO-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,140982  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,292474  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,036485

C1 -0.2867902200 0.7010650252  
 -1.8489976140  
 O2 1.0466187750 1.1716739232  
 -2.3922084387

|                                 |                             |
|---------------------------------|-----------------------------|
| C3 -0.0473495626 -0.2543488792  | H23 5.6269188161            |
| -0.7322326876                   | 0.6575463032 -1.1175491483  |
| Si4 -0.9454602434 -0.1209737862 | H24 3.8127776789            |
| 0.8480063856                    | 0.8559474256 2.5169010689   |
| B5 1.9387586410 0.9190063811    | H25 2.6598416289            |
| -1.3516802739                   | 2.1951606822 2.3419224697   |
| O6 2.1388007105 1.7849323702    | H26 2.1190089748            |
| -0.2755497979                   | 0.5334479315 2.0821384156   |
| C7 3.3136360779 1.3633480898    | H27 3.6760604187            |
| 0.4582645039                    | -1.3830727450 1.4438429837  |
| C8 3.7303541561 0.0003946846    | H28 2.1208615041            |
| -0.2516868948                   | -1.1962839637 0.5789539102  |
| O9 3.0502749825 0.0806465774    | H29 3.4331369137            |
| -1.5374106764                   | -2.1332460302 -0.1482469950 |
| C10 4.3503818593                | H30 -2.9763475083           |
| 2.4829742423 0.3018422179       | -1.5768054453 0.4399707912  |
| C11 5.2306211239                | H31 -3.2634014567           |
| -0.1483044342 -0.4939940007     | -0.4965078861 1.8256952524  |
| C12 2.9537990857                | H32 -3.3790127258           |
| 1.2189769233 1.9393179853       | 0.1238009749 0.1625420632   |
| C13 3.2039922273                | H33 -0.9157943563           |
| -1.2527381506 0.4631675147      | -1.3492925392 3.0419288727  |
| C14 -2.8202062016               | H34 -0.2058589569           |
| -0.5571080240 0.8193862304      | -2.3515790095 1.7623745738  |
| C15 -0.2577542791               | H35 0.7476099577            |
| -1.3291774486 2.1616343327      | -1.0588659042 2.5034506244  |
| C16 -0.8983099323               | H36 -1.4016502775           |
| 1.6433051268 1.5715351146       | 2.3559108025 0.9034656030   |
| H17 0.0882367984                | H37 -1.4161855792           |
| -1.2832113952 -1.0887399425     | 1.6764965970 2.5408325066   |
| H18 5.2658668673                | H38 0.1308901648            |
| 2.2680901414 0.8654238070       | 1.9895386560 1.7090471162   |
| H19 4.6091681872                | C39 -2.6857166400           |
| 2.6396317997 -0.7503795617      | -1.2320522465 -4.8912000454 |
| H20 3.9210888530                | C40 -1.2994254427           |
| 3.4150119353 0.6874632077       | -1.4363222031 -4.8557615025 |
| H21 5.7721124973                | C41 -0.5084323362           |
| -0.1501492533 0.4601562209      | -0.7643893473 -3.9188777987 |
| H22 5.4301479588                | C42 -1.0857814878           |
| -1.1024095049 -0.9955195554     | 0.1157994034 -2.9888386098  |

C43 -2.4741530374  
 0.3280008238 -3.0458617765  
 C44 -3.2685970639  
 -0.3391591736 -3.9810811789  
 H45 -3.3029849258  
 -1.7587408604 -5.6162219748  
 H46 -0.8352767152  
 -2.1273134499 -5.5580409016  
 H47 0.5647357713  
 -0.9326411750 -3.8794034565  
 H48 -2.9372047851  
 1.0019887762 -2.3261428179  
 H49 -4.3437398103  
 -0.1671237236 -3.9988395267  
 H50 -0.7854057798  
 1.6157402654 -1.5013321734  
 Li51 3.5928054852  
 0.4358130024 -4.5846666310

#### 9.3.2.12. *TSelimBO-cis*

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,138970  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,292464  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,034260

C1 -0.2750388352 0.9739450024  
 -1.8061988606  
 O2 1.0591236250 1.6741399918  
 -1.7978993440  
 C3 -0.4148648903 0.2198136694  
 -0.5249328516  
 C4 -1.3449499009 2.0175209762  
 -2.0587880110  
 C5 -2.5578906641 1.6198377586  
 -2.6491482777  
 C6 -3.6215577967 2.5111717065  
 -2.7819874697

C7 -3.4976858503 3.8306746595  
 -2.3209654250  
 C8 -2.2900453293 4.2419403552  
 -1.7495853886  
 C9 -1.2202844802 3.3454413671  
 -1.6307925106  
 Si10 -1.1864476245  
 0.7878133843 1.0227529940  
 B11 1.7938207484  
 0.9037024264 -0.9019119018  
 O12 2.4439708705  
 1.4788767501 0.1992210039  
 C13 3.4682093217  
 0.5496237091 0.6616245106  
 C14 3.1187410534  
 -0.7984915201 -0.0960866076  
 O15 2.4040612312  
 -0.3145065640 -1.2574112034  
 C16 4.8230572085  
 1.1277886265 0.2406219551  
 C17 4.3312131259  
 -1.6049551747 -0.5659919985  
 C18 3.3854697108  
 0.4498542030 2.1838980914  
 C19 2.1930513070  
 -1.7323668250 0.6975507306  
 C20 -1.0066136765  
 -0.5694481672 2.3572720000  
 C21 -0.3741837045  
 2.3555619245 1.7731163566  
 C22 -3.0617855108  
 1.1924622803 1.0058036138  
 H23 -0.2438405545  
 0.2983377130 -2.6716700974  
 H24 -0.3239006940  
 -0.8629228410 -0.6349837555  
 H25 -2.6705043205  
 0.5865955568 -2.9752057220  
 H26 -4.5534821553  
 2.1774403069 -3.2350460750

H27 -4.3299778664  
 4.5254270798 -2.4127297720  
 H28 -2.1767140234  
 5.2659677777 -1.3962276672  
 H29 -0.2786329793  
 3.6630278887 -1.1941582857  
 H30 5.6543366625  
 0.5082638449 0.5967415334  
 H31 4.8890773836  
 1.2111309530 -0.8490250189  
 H32 4.9332686807  
 2.1299206130 0.6712912833  
 H33 4.9465730308  
 -1.9123788854 0.2890297759  
 H34 3.9846878369  
 -2.5117336947 -1.0758333382  
 H35 4.9549719996  
 -1.0424057423 -1.2659552538  
 H36 4.0871107216  
 -0.3041834129 2.5613519083  
 H37 3.6464688758  
 1.4135699455 2.6369320150  
 H38 2.3774967292  
 0.1830354271 2.5103462400  
 H39 2.7091396471  
 -2.1654099457 1.5619788532  
 H40 1.2989235909  
 -1.2085669715 1.0291855038  
 H41 1.8725843388  
 -2.5508463406 0.0426808571  
 H42 -1.6190472346  
 -0.3266430666 3.2371759092  
 H43 -1.3411319182  
 -1.5436376296 1.9746233140  
 H44 0.0305702222  
 -0.6862705724 2.6948563203  
 H45 -0.7769372549  
 2.5752260688 2.7726702874  
 H46 0.7100211490  
 2.2089736111 1.8414147144

H47 -0.5614431409  
 3.2274844369 1.1328302609  
 H48 -3.4048608623  
 1.5288702440 1.9962342415  
 H49 -3.2972410802  
 1.9744838555 0.2728958541  
 H50 -3.6401844929  
 0.2991240047 0.7310593552  
 Li51 2.4120114243  
 4.6024023522 0.6409443915

### 9.3.2.13. TScycleSiO-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,148259  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,310377  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,052912

C1 -0.4002225619 -1.1238960388  
 -1.3076726517  
 O2 0.4646624561 -2.2040111102  
 -1.5654637675  
 Li3 1.7192929794 -3.2216220953  
 -4.1480695776  
 C4 0.0986047381 -0.5251421090  
 0.0417855152  
 C5 -0.3849775073 -0.0246399694  
 -2.3635694360  
 C6 -1.5120273399 0.7793710800  
 -2.5898322730  
 C7 -1.4475960530 1.8894975470  
 -3.4397401030  
 C8 -0.2469584913 2.2128501341  
 -4.0838351632  
 C9 0.8817074275 1.4080045799  
 -3.8763309512  
 C10 0.8078832908  
 0.2987661314 -3.0281317228

|                             |                             |
|-----------------------------|-----------------------------|
| Si11 1.3801642782           | H31 -1.6742925971           |
| -1.9365608413 0.3690542840  | 0.4980641707 5.1446966577   |
| B12 -0.9130255617           | H32 -0.4943817626           |
| -0.1979834833 1.1704524508  | -0.3996404266 4.1612551561  |
| O13 -0.9048707491           | H33 -0.2915180940           |
| 0.9896456729 1.8928989843   | 1.3418962182 4.4154468446   |
| C14 -1.8465406061           | H34 -3.8037681557           |
| 0.8701046982 3.0006517001   | -0.7171817506 4.3946266158  |
| C15 -2.7768333519           | H35 -3.8501248793           |
| -0.3141006233 2.5271909787  | -2.0531718576 3.2253389962  |
| O16 -1.9218912350           | H36 -2.3649129119           |
| -1.0450614990 1.6002121529  | -1.7301730713 4.1359060004  |
| C17 -1.0305921310           | H37 -3.3417379962           |
| 0.5484694529 4.2592728619   | 2.1185364387 3.9562494396   |
| C18 -3.2190562351           | H38 -1.8478097432           |
| -1.2601890528 3.6419058536  | 2.9687166149 3.5157625310   |
| C19 -2.5640717888           | H39 -3.0274748739           |
| 2.2070147996 3.1875707980   | 2.5529254207 2.2601118280   |
| C20 -3.9978686347           | H40 -4.7215445680           |
| 0.1527999401 1.7240010566   | 0.6719906563 2.3621434421   |
| C21 1.9792950898            | H41 -3.7059282854           |
| -1.3281789593 2.1459161160  | 0.8229441680 0.9085086022   |
| C22 0.7885559405            | H42 -4.4877190458           |
| -3.6742626241 0.8737572561  | -0.7236420267 1.2862191096  |
| C23 3.0718882130            | H43 2.8185800051            |
| -1.8353675255 -0.5155611758 | -1.9305259297 2.5277433553  |
| H24 -1.4503945348           | H44 2.3038074339            |
| -1.4595442296 -1.1906956366 | -0.2761477035 2.1247996468  |
| H25 0.7194864509            | H45 1.1670445868            |
| 0.3652251435 -0.1362094208  | -1.3919926951 2.8855214068  |
| H26 -2.4429119492           | H46 1.4151876023            |
| 0.5458810801 -2.0736727822  | -4.0861416548 1.6769867531  |
| H27 -2.3308151606           | H47 -0.2366296287           |
| 2.5077769013 -3.5928089447  | -3.5930107513 1.2614632316  |
| H28 -0.1905416080           | H48 0.7759319707            |
| 3.0828182021 -4.7352765808  | -4.3685369768 0.0269894076  |
| H29 1.8226887958            | H49 3.9011114920            |
| 1.6571652863 -4.3649380301  | -2.0743713737 0.1651223510  |
| H30 1.6823485271            | H50 3.1140166787            |
| -0.3180875561 -2.8357687291 | -2.4942609395 -1.3900204511 |



H51 3.2203519199  
-0.8046277249 -0.8688511585

#### 9.3.2.14. TScycleSiO-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
-1.212,146449  
E(LCCSD/6-311+G(d,p)(THF)) =  
-1212,158949  
G(LCCSD/6-311+G(d,p)(THF)) =  
-1211,892119

C1 -0.5312757410 0.1240249120  
-2.2275349811  
C2 -0.4138951460 0.1326388662  
-0.6648083902  
O3 -1.5074322458 -0.8528232450  
-2.5079147827  
Si4 -2.0694368085 -0.7982583067  
-0.3095128662  
B5 -0.1178030273 1.3939212587  
0.2177486830  
O6 0.9558670441 1.4607250893  
1.1055387982  
C7 0.7620254302 2.6192533459  
1.9788063522  
C8 -0.2384768131 3.5078180054  
1.1425731233  
O9 -0.8976815835 2.5282559320  
0.2914150394  
C10 0.1727265294  
2.1062355004 3.2997686306  
C11 -1.3009566504  
4.2302718453 1.9708567533  
C12 2.1177818701  
3.2699322766 2.2510257281  
C13 0.4647728212  
4.5133082603 0.2231150784  
C14 -2.1794148625  
-0.4846532750 1.6252507816

C15 -3.7673353857  
-0.0601058980 -0.7664695097  
C16 -2.0368738662  
-2.7055093942 -0.2952324565  
H17 0.4493488387  
-0.1616116133 -2.6620004695  
H18 0.3325743392  
-0.6314908533 -0.3904211829  
H19 0.0439907982  
2.9274558552 4.0143146442  
H20 -0.7938910200  
1.6196925179 3.1489281854  
H21 0.8585378143  
1.3732752127 3.7390357520  
H22 -0.8309200717  
4.9207446953 2.6827354557  
H23 -1.9466901308  
4.8129850323 1.3044652613  
H24 -1.9303196392  
3.5299129048 2.5259493700  
H25 1.9848662188  
4.1916852635 2.8313427508  
H26 2.7460872577  
2.5902347725 2.8378758475  
H27 2.6475005820  
3.5144032179 1.3266787656  
H28 0.9316605285  
5.3154715262 0.8062182855  
H29 1.2332339644  
4.0316219929 -0.3887383725  
H30 -0.2738589566  
4.9541624400 -0.4530739905  
H31 -2.9949120605  
-1.0546028045 2.0979691214  
H32 -1.2431956226  
-0.7477862976 2.1402779761  
H33 -2.3657281054  
0.5809163691 1.8238160604  
H34 -4.4959213140  
-0.3498023666 0.0045403474

H35 -3.7038377515  
 1.0355412689 -0.7689660213  
 H36 -4.1354289317  
 -0.3819835474 -1.7462059378  
 H37 -1.0339142563  
 -3.0512819626 -0.0042849493  
 H38 -2.7438557075  
 -3.0886094644 0.4542232498  
 H39 -2.2723688159  
 -3.1371998390 -1.2751396916  
 C40 -1.4422453370  
 4.1406001856 -3.6347638814  
 C41 -0.1435729155  
 3.8058986275 -3.2302315991  
 C42 0.1436318494  
 2.5060129570 -2.8113565557  
 C43 -0.8495024009  
 1.5145014031 -2.7829723337  
 C44 -2.1356898732  
 1.8528333340 -3.2124312285  
 C45 -2.4357560571  
 3.1562585429 -3.6279200941  
 H46 -1.6754479979  
 5.1578113371 -3.9451628375  
 H47 0.6378586695  
 4.5639320154 -3.2243676111  
 H48 1.1489063842  
 2.2606945293 -2.4682565292  
 H49 -2.8945858181  
 1.0777757481 -3.2018536380  
 H50 -3.4487083163  
 3.4066856985 -3.9397680037  
 Li51 -3.1702397557  
 -2.0261926600 -4.4212707675

### 9.3.2.15. SiOcycle-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1212,151916

E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,304297  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,056409

C1 0.7312439799 0.5898467079  
 -2.0100344831  
 C2 0.7496650215 -0.1091231503  
 -0.6574018653  
 C3 0.3809618854 -0.3549042921  
 -3.1395027579  
 C4 1.3891269117 -0.9943401177  
 -3.8767602786  
 C5 1.0740102735 -1.9740959332  
 -4.8236350350  
 C6 -0.2619586238 -2.3288129353  
 -5.0523099802  
 C7 -1.2764336660 -1.6872539506  
 -4.3298234986  
 C8 -0.9550528898 -0.7070715345  
 -3.3858215883  
 Si9 -0.4929471143 1.4899614679  
 -0.0273917136  
 B10 2.0306454145  
 -0.4309725284 0.1075249623  
 O11 2.1189561951  
 -1.4985141988 1.0140046346  
 C12 3.3477608631  
 -1.3561458664 1.7770106035  
 C13 4.2304536582  
 -0.4677164479 0.8219394969  
 O14 3.2338892998  
 0.2752442569 0.0663404687  
 C15 2.9896491161  
 -0.6652947379 3.1004842510  
 C16 5.1483137296  
 0.5179343016 1.5431680185  
 C17 3.9224230091  
 -2.7435814021 2.0646601856

C18 5.0397817949  
 -1.2905936443 -0.1904019387  
 C19 0.7740514841  
 2.5909623155 0.8945738502  
 C20 -2.0589051902  
 2.6533172614 -0.2362003369  
 C21 -1.3276254440  
 0.3594382840 1.3200354702  
 H22 1.7010510058  
 1.0653680993 -2.2281583205  
 H23 0.0785933532  
 -0.9782920073 -0.6599248580  
 H24 2.4303104335  
 -0.7346970745 -3.6884639655  
 H25 1.8704309180  
 -2.4658551746 -5.3793828917  
 H26 -0.5088233622  
 -3.0976777412 -5.7816050348  
 H27 -2.3176421933  
 -1.9608334079 -4.4949872338  
 H28 -1.7342481993  
 -0.2173273555 -2.8064049944  
 H29 3.8652749107  
 -0.5748752920 3.7536006509  
 H30 2.5747857100  
 0.3331600077 2.9306894923  
 H31 2.2334812658  
 -1.2652270344 3.6189018154  
 H32 5.8520024952  
 -0.0181666149 2.1924077082  
 H33 5.7286849348  
 1.0893241286 0.8097715202  
 H34 4.5800268862  
 1.2255946258 2.1521746805  
 H35 4.9004084683  
 -2.6598053182 2.5550933092  
 H36 3.2515606879  
 -3.2913173851 2.7365478934  
 H37 4.0403394851  
 -3.3305569473 1.1499622230

H38 5.8552154055  
 -1.8372169139 0.2969850917  
 H39 4.4021543586  
 -2.0082738359 -0.7175931150  
 H40 5.4743486369  
 -0.6109389222 -0.9316669265  
 H41 0.2937929367  
 3.4626125517 1.3615276928  
 H42 1.2798702244  
 2.0156616601 1.6811200992  
 H43 1.5568160859  
 2.9516528027 0.2145857204  
 H44 -2.3748294089  
 3.0620012734 0.7347915779  
 H45 -1.8688365751  
 3.4912307593 -0.9248832948  
 H46 -2.9079513238  
 2.0805477364 -0.6429231264  
 H47 -1.9018215647  
 0.9383831454 2.0598485135  
 H48 -2.0172952131  
 -0.3586477453 0.8502494400  
 H49 -0.5596329795  
 -0.2259348813 1.8445562179  
 O50 -0.2758016507  
 1.6117502394 -1.8318686182  
 Li51 -2.5850622501  
 2.6814079041 -3.8483260969

### 9.3.2.16. SiOcycle-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1212,147139  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,305353  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,051626

C1 3.6270452436 1.6730676979  
 -0.7033008891

|                               |                            |
|-------------------------------|----------------------------|
| O2 2.5509561765 2.6099841880  | H22 3.5625303224           |
| -0.9855436372                 | -2.6248975350 4.4300538915 |
| C3 3.0551410110 0.7783025415  | H23 5.1213884067           |
| 0.3825728084                  | -2.4086231256 3.6131106493 |
| Si4 1.4362608076 2.3155391369 | H24 5.5377094112           |
| 0.3757209940                  | 0.8641949932 5.6699752106  |
| B5 3.6991026304 0.4387281124  | H25 6.0563035212           |
| 1.7149794074                  | 2.1359840739 4.5411672167  |
| O6 4.5594586332 1.2451667652  | H26 4.3478141050           |
| 2.4596277905                  | 1.9985525122 4.9865202773  |
| C7 5.0507697259 0.4833402674  | H27 3.0597381662           |
| 3.5848594341                  | 0.0035277031 5.7014878593  |
| C8 3.9214939549 -0.5919121608 | H28 2.3953303255           |
| 3.7803046805                  | 0.8807942798 4.3014120810  |
| O9 3.4159643236 -0.7492898992 | H29 1.9341779611           |
| 2.4253713333                  | -0.8077483702 4.5918747687 |
| C10 6.3983532282              | H30 -0.8356471005          |
| -0.1256576126 3.1689121681    | 1.3610628272 1.0478467934  |
| C11 4.4109849802              | H31 -0.0138950292          |
| -1.9426311976 4.3014557135    | 0.2893457585 -0.1077575698 |
| C12 5.2536183471              | H32 0.5071151831           |
| 1.4257868851 4.7707404514     | 0.3035663801 1.5832241012  |
| C13 2.7601844234              | H33 0.9857977172           |
| -0.0903400555 4.6509321160    | 3.1747635837 2.6740721225  |
| C14 0.1409569944              | H34 2.7373456122           |
| 0.9388371379 0.7658157157     | 2.9049569736 2.5052723591  |
| C15 1.8430272137              | H35 1.9748120912           |
| 3.2671927776 1.9900426316     | 4.3386004869 1.7817791463  |
| C16 0.1766211253              | H36 -0.6172857563          |
| 3.5878568476 -0.4155217000    | 3.8423998229 0.3028392318  |
| H17 2.5531083919              | H37 0.6796022646           |
| -0.0926821806 -0.0574055271   | 4.5214656924 -0.7158209649 |
| H18 6.8758440261              | H38 -0.3115388665          |
| -0.6573223897 4.0005230138    | 3.1691388391 -1.3090961852 |
| H19 6.2742633266              | C39 7.3398679356           |
| -0.8213363347 2.3321222116    | 3.6233895075 0.4102545627  |
| H20 7.0604913066              | C40 6.1235747915           |
| 0.6821920638 2.8404807150     | 4.2951521319 0.5696324402  |
| H21 4.8988874050              | C41 4.9242623988           |
| -1.8217531362 5.2772700678    | 3.6814880333 0.1927330427  |

C42 4.9165650609  
 2.3897840121 -0.3453816868  
 C43 6.1423632544  
 1.7266186601 -0.5072138799  
 C44 7.3434787647  
 2.3311648646 -0.1323742985  
 H45 8.2740604574  
 4.0977302903 0.7048963848  
 H46 6.1069073786  
 5.2964057117 0.9979762661  
 H47 3.9778204282  
 4.1917563569 0.3397634950  
 H48 6.1472598093  
 0.7146701513 -0.9115368159  
 H49 8.2827345226  
 1.7953524644 -0.2596793623  
 H50 3.8178057381  
 1.1060776672 -1.6303353842  
 Li51 2.9974126107  
 5.4772584595 -2.3808549138

### 9.3.2.17. OpenInt-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,160561  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,306504  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,059224

C1 3.7877734072 1.3900348195  
 -1.3121760796  
 O2 2.7287031060 2.4504506325  
 -1.3278592028  
 C3 3.3727368520 0.0454728817  
 -0.8314847601  
 Si4 1.3429961538 2.4208657683  
 -0.3915882494  
 B5 3.6521081053 -0.3913357286  
 0.5453473609

O6 4.2489057954 0.4399735763  
 1.5373761572  
 C7 4.5436813125 -0.3527832239  
 2.6967209464  
 C8 3.5103371558 -1.5328693453  
 2.5643882794  
 O9 3.3661430521 -1.6695771143  
 1.1294802298  
 C10 6.0059490413  
 -0.8148139144 2.5914331689  
 C11 3.9883453406  
 -2.8563033649 3.1587666312  
 C12 4.3708895551  
 0.5137550091 3.9473325977  
 C13 2.1296044398  
 -1.1701103376 3.1337576927  
 C14 0.2027756641  
 0.9337015586 -0.6897749392  
 C15 1.6972207342  
 2.6098095034 1.4549633583  
 C16 0.3997655477  
 3.9576399500 -0.9683929855  
 H17 2.8015855579  
 -0.5538033548 -1.5476885788  
 H18 6.3279873065  
 -1.3692270683 3.4808588596  
 H19 6.1536944424  
 -1.4449067156 1.7081793027  
 H20 6.6445504123  
 0.0697446103 2.4867235186  
 H21 4.2053757610  
 -2.7413021071 4.2286175589  
 H22 3.2096537384  
 -3.6211488015 3.0509625150  
 H23 4.8918990438  
 -3.2163796846 2.6585799584  
 H24 4.4944774949  
 -0.0823566111 4.8605023892  
 H25 5.1295538101  
 1.3058283358 3.9534370157

H26 3.3890718950  
 0.9938190949 3.9708900501  
 H27 2.1433977691  
 -1.1031491153 4.2279347548  
 H28 1.7796859989  
 -0.2155007269 2.7281918986  
 H29 1.4133984089  
 -1.9482707156 2.8452523540  
 H30 -0.8186160727  
 1.1788224407 -0.3619257860  
 H31 0.1699958012  
 0.6824206135 -1.7581156669  
 H32 0.5591287907  
 0.0537195853 -0.1459343020  
 H33 1.9595338984  
 3.6519881257 1.6848233982  
 H34 0.8085178551  
 2.3503074010 2.0481339813  
 H35 2.5255466324  
 1.9668529451 1.7680415285  
 H36 -0.5257392701  
 4.0819293459 -0.3883979893  
 H37 1.0073350826  
 4.8622171207 -0.8338120174  
 H38 0.1285533675  
 3.8853364809 -2.0300609945  
 Li39 0.7854734733  
 -2.7868902457 -0.9111822365  
 C40 5.4849957020  
 1.2175418986 -5.3094458662  
 C41 4.1166527212  
 1.4568957503 -5.1390588820  
 C42 3.5680404885  
 1.5412720800 -3.8533106264  
 C43 4.3701950921  
 1.3703319797 -2.7149299290  
 C44 5.7424121144  
 1.1305641446 -2.8981132886  
 C45 6.2983139667  
 1.0599713727 -4.1779003531

H46 5.9162211710  
 1.1657049736 -6.3072119271  
 H47 3.4753285105  
 1.5922491916 -6.0089271332  
 H48 2.5126611285  
 1.7621729484 -3.7201632256  
 H49 6.3757898786  
 0.9967276413 -2.0218642163  
 H50 7.3668206937  
 0.8864081310 -4.2951927761  
 H51 4.5515524867  
 1.7859571748 -0.6316491220

### 9.3.2.18. OpenInt-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,154871  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,302133  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,046470

C1 4.3283708487 1.0314007550  
 -0.2418467915  
 O2 3.0669731380 1.7920189427  
 -0.6282153755  
 C3 4.0797574467 -0.2981065613  
 0.3444950165  
 Si4 1.7068431986 1.8508884550  
 0.3732902898  
 B5 4.1133183684 -0.7442428507  
 1.7466874902  
 O6 4.5086009143 0.0002377166  
 2.8829698022  
 C7 4.6611855450 -0.8962597685  
 3.9911155451  
 C8 3.6635967970 -2.0488882745  
 3.6142139775  
 O9 3.7429809221 -2.0627543438  
 2.1733586327

|                             |                             |
|-----------------------------|-----------------------------|
| C10 6.1290240798            | H30 -0.3574360307           |
| -1.3535765131 4.0094094442  | 0.5610080611 0.8357073646   |
| C11 4.0423945347            | H31 0.4505176559            |
| -3.4268019427 4.1542702512  | -0.0799961884 -0.6174895998 |
| C12 4.3325566543            | H32 1.0764277291            |
| -0.1396729058 5.2781335221  | -0.4882521136 0.9924223827  |
| C13 2.2132622057            | H33 1.1447411868            |
| -1.7090956809 3.9972893041  | 2.2965287352 2.7398965658   |
| C14 0.6191613102            | H34 2.8163219961            |
| 0.3060189120 0.3961152220   | 1.7035303675 2.6309561645   |
| C15 2.0764850865            | H35 2.4475282859            |
| 2.3554267014 2.1575353730   | 3.3869296606 2.2116037814   |
| C16 0.6750628309            | H36 -0.2375967523           |
| 3.2515478715 -0.3872395148  | 3.4052580774 0.2068841813   |
| H17 3.6264737280            | H37 1.2323451388            |
| -0.9824353063 -0.3830146063 | 4.1979281791 -0.3964668493  |
| H18 6.3477541769            | H38 0.3705368460            |
| -1.9920814428 4.8732603627  | 3.0273941710 -1.4176707535  |
| H19 6.3775672208            | C39 7.0769820577            |
| -1.9023293509 3.0944890056  | 3.7437893619 1.8045875914   |
| H20 6.7722742821            | C40 7.3489019644            |
| -0.4679312597 4.0593440475  | 2.3733048408 1.7201899285   |
| H21 4.1047123894            | C41 6.4511384777            |
| -3.4086233455 5.2499913333  | 1.5117535630 1.0844559700   |
| H22 3.2806975854            | C42 5.2607367326            |
| -4.1623706123 3.8690493620  | 1.9882390712 0.5129950317   |
| H23 5.0040857398            | C43 5.0066768119            |
| -3.7624894390 3.7555130018  | 3.3664326729 0.5971526212   |
| H24 4.3347132418            | C44 5.8974350645            |
| -0.8169931307 6.1418356862  | 4.2348047730 1.2385056605   |
| H25 5.0856511053            | H45 7.7690418313            |
| 0.6392626508 5.4494559209   | 4.4152020234 2.3096124430   |
| H26 3.3560421284            | H46 8.2564944422            |
| 0.3480851979 5.2149096618   | 1.9706966303 2.1663634743   |
| H27 2.0615673045            | H47 6.6485069364            |
| -1.7431069918 5.0828258290  | 0.4458465998 1.0575124235   |
| H28 1.9382640740            | H48 4.0930255095            |
| -0.7126543865 3.6353367767  | 3.7573363895 0.1664680226   |
| H29 1.5407424980            | H49 5.6614806387            |
| -2.4384266298 3.5322056916  | 5.2961530519 1.3038750143   |

H50 4.7824355981  
0.9513850005 -1.2439482865  
Li51 4.0522440113  
3.6132616582 -3.0525667465

#### 9.3.2.19. TSelimSiO-trans

E(B3LYP-D3/6-31+G(d)(THF)) =  
-1.212,155915  
E(LCCSD/6-311+G(d,p)(THF)) =  
-1208,288780  
G(LCCSD/6-311+G(d,p)(THF)) =  
-1208,042418

C1 4.3248556021 0.4639962836  
-1.3662278505  
O2 3.3836129857 2.0264657155  
-1.0893318989  
C3 3.8765070739 -0.7250999154  
-0.7443921193  
Si4 1.7909616885 1.9822039014  
-0.6675177835  
B5 3.9650205035 -1.1243556452  
0.7006561346  
O6 4.3616367874 -0.3431391360  
1.7955784998  
C7 4.3887491956 -1.1810127735  
2.9801789441  
C8 3.4420865892 -2.3777622266  
2.5840775968  
O9 3.5674756054 -2.4080349122  
1.1416212422  
C10 5.8450568759  
-1.6127469862 3.1986446640  
C11 3.8578634111  
-3.7339246386 3.1555396459  
C12 3.9014428723  
-0.3594721583 4.1734288968  
C13 1.9616307099  
-2.1204225667 2.9074335120

C14 0.7594510512  
0.5892399164 -1.4515810597  
C15 1.5193046911  
1.8514767358 1.2065592874  
C16 0.9830432667  
3.5957010561 -1.2745674935  
H17 3.2487108798  
-1.3857791788 -1.3443082069  
H18 5.9604338766  
-2.2053916501 4.1135912514  
H19 6.2091136193  
-2.2015032184 2.3500563589  
H20 6.4707532458  
-0.7173053715 3.2857246423  
H21 3.8605627177  
-3.7055354653 4.2526428910  
H22 3.1452159636  
-4.5040367511 2.8378070539  
H23 4.8524518928  
-4.0309461530 2.8120228891  
H24 3.8188814067  
-0.9887048977 5.0685757418  
H25 4.6127290025  
0.4467832685 4.3869102996  
H26 2.9273689467  
0.0944119182 3.9741002417  
H27 1.7751211903  
-2.1302591711 3.9875495061  
H28 1.6263028263  
-1.1613679458 2.5009825132  
H29 1.3588762571  
-2.9119691719 2.4481131195  
H30 -0.2990663020  
0.7444615253 -1.1968221704  
H31 0.8438247611  
0.5764712086 -2.5449214977  
H32 1.0572983230  
-0.3949830895 -1.0751644667  
H33 1.8510191021  
2.7570995140 1.7324561526



H34 0.4576269787  
 1.6895363869 1.4436692913  
 H35 2.0962071538  
 1.0098350106 1.6059487009  
 H36 -0.0882415988  
 3.6198836142 -1.0251281751  
 H37 1.4532083701  
 4.4836354811 -0.8308715826  
 H38 1.0765292140  
 3.6684362302 -2.3677271546  
 C39 4.2872588355  
 0.7767740258 -5.6957013735  
 C40 3.3912608442  
 -0.0799708565 -5.0446988369  
 C41 3.4073979345  
 -0.1926857524 -3.6532194022  
 C42 4.3101357808  
 0.5464352243 -2.8672608699  
 C43 5.2050350309  
 1.3994841449 -3.5360486699  
 C44 5.1978265049  
 1.5160200220 -4.9302837861  
 H45 4.2819464853  
 0.8574437228 -6.7809821211  
 H46 2.6802326409  
 -0.6704736269 -5.6209629857  
 H47 2.7019881386  
 -0.8648719532 -3.1766791579  
 H48 5.9177647911  
 1.9763501369 -2.9483819536  
 H49 5.9119619640  
 2.1737971983 -5.4230960413  
 H50 5.2018851536  
 0.9310621648 -0.9212929382  
 Li51 4.0687278546  
 4.8224927704 -3.0154664880

### 9.3.2.20. TSelimSiO-cis

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -1.212,151689  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,293914  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -1208,043423  
  
 C1 4.8705011615 1.5389288493  
 0.3557178838  
 O2 3.3594315455 2.2972480946  
 -0.0047680265  
 C3 4.7329804321 0.2154391140  
 0.9187877392  
 Si4 2.2507050530 2.6706904495  
 1.1756031142  
 B5 4.5590186647 -0.2180743927  
 2.3379597312  
 O6 4.6439629685 0.5768681011  
 3.4940838229  
 C7 4.8193268214 -0.2801270354  
 4.6359720697  
 C8 4.1101021029 -1.6008572213  
 4.1624723342  
 O9 4.3134684298 -1.5706657065  
 2.7239231849  
 C10 6.3314324587  
 -0.4514056351 4.8627353737  
 C11 4.7165510098  
 -2.8823964188 4.7309534130  
 C12 4.1967923416  
 0.3924488249 5.8605519783  
 C13 2.5972475905  
 -1.5763522212 4.4215686957  
 C14 1.1939283620  
 1.1621227969 1.6494256687  
 C15 2.9815164727  
 3.3782892813 2.7720448999

C16 1.0879596231  
 3.9960149597 0.4719103705  
 H17 4.4708097407  
 -0.5316073480 0.1597301120  
 H18 6.5438240485  
 -1.0485586801 5.7570909332  
 H19 6.8102334639  
 -0.9285183765 4.0005686575  
 H20 6.7805815166  
 0.5389021276 4.9970997785  
 H21 4.6774792599  
 -2.8721863970 5.8277421854  
 H22 4.1532695326  
 -3.7550998237 4.3795150027  
 H23 5.7588251801  
 -3.0027415940 4.4225386862  
 H24 4.2278528136  
 -0.2739266271 6.7318608094  
 H25 4.7631154261  
 1.2991037488 6.1032174574  
 H26 3.1602616712  
 0.6863562435 5.6765247746  
 H27 2.3693598005  
 -1.6709841248 5.4898224068  
 H28 2.1526489952  
 -0.6480032754 4.0516411524  
 H29 2.1310199957  
 -2.4170203696 3.8946626167  
 H30 0.4541893436  
 1.4126538568 2.4231401161  
 H31 0.6575559305  
 0.7678809772 0.7748291340  
 H32 1.8439407346  
 0.3718101890 2.0390186698  
 H33 2.1643592512  
 3.6039298576 3.4734505527  
 H34 3.6611597291  
 2.6691738929 3.2537779625  
 H35 3.5346293779  
 4.3058595641 2.5795144116

H36 0.3070598864  
 4.2517561169 1.2033517773  
 H37 1.6457756295  
 4.9141760366 0.2419830524  
 H38 0.5930374201  
 3.6606984239 -0.4490312205  
 C39 7.2084983486  
 4.7201288606 2.2113553401  
 C40 7.3229063432  
 3.4053275675 2.6716263017  
 C41 6.5742716376  
 2.3780028371 2.0845294002  
 C42 5.6770078978  
 2.6360597517 1.0379132663  
 C43 5.5921292968  
 3.9619641026 0.5697280726  
 C44 6.3411251247  
 4.9911705156 1.1454647511  
 H45 7.7882927842  
 5.5195028824 2.6699040359  
 H46 7.9974146816  
 3.1733882511 3.4944561605  
 H47 6.6741129939  
 1.3684730586 2.4589434648  
 H48 4.9032408780  
 4.1856654645 -0.2383007132  
 H49 6.2429777334  
 6.0074224025 0.7665451295  
 H50 5.1484377685  
 1.5198116058 -0.7007712360  
 Li51 1.9448295390  
 -2.2370375634 0.2044712538

### 9.3.2.21. 222-Z

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -720,141273  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -717,666828

G(LCCSD/6-311+G(d,p)(THF)) =  
-717,411772

C1 -4.7952576191 1.1799545491  
-0.4396126283  
C2 -3.4125537362 1.1821073349  
-0.6338777812  
C3 -2.5483795465 0.6451045471  
0.3437760647  
C4 -3.1271607552 0.1127749433  
1.5177266566  
C5 -4.5104749576 0.1116258471  
1.7110856060  
C6 -5.3529523369 0.6466849578  
0.7301745100  
C7 -1.0795715472 0.5913479707  
0.2411021743  
C8 -0.1995874048 0.9580276150  
-0.7269510297  
B9 -0.3031880822 1.5727797802  
-2.1499158308  
O10 -1.4137014280  
2.0267946856 -2.8222644126  
C11 -1.0264012532  
2.2933355334 -4.2090688558  
C12 0.5250840241  
2.5202092869 -4.0764602333  
O13 0.8534779775  
1.7150337620 -2.8988630602  
C14 1.3498178177  
2.0232123654 -5.2602758578  
C15 0.8981466387  
3.9688113520 -3.7374993421  
C16 -1.3950523611  
1.0414904279 -5.0142875540  
C17 -1.8154906190  
3.4985475172 -4.7123723729  
H18 -5.4436695965  
1.5988961299 -1.2071216607

H19 -3.0033074098  
1.5953529840 -1.5468096096  
H20 -2.4803973145  
-0.3060188234 2.2875219936  
H21 -4.9296445639  
-0.3061893611 2.6241373272  
H22 -6.4315390279  
0.6477011890 0.8743847794  
H23 -0.6301707564  
0.1623394663 1.1405155729  
H24 0.8423419793  
0.7638799753 -0.4574021544  
H25 1.0525795998  
2.5477854598 -6.1764131117  
H26 2.4124653410  
2.2224932890 -5.0823824971  
H27 1.2267450031  
0.9482472866 -5.4165927269  
H28 0.7299043600  
4.6321263389 -4.5929662350  
H29 0.3164600131  
4.3403135370 -2.8868344685  
H30 1.9599202962  
4.0108137286 -3.4715681806  
H31 -1.1878788946  
1.1820325617 -6.0806954094  
H32 -0.8431857811  
0.1633715181 -4.6619351319  
H33 -2.4654290269  
0.8441463290 -4.8933542228  
H34 -1.4737953696  
3.7853646451 -5.7142690664  
H35 -2.8794672172  
3.2445314009 -4.7742311060  
H36 -1.7084590463  
4.3577699203 -4.0452977280

### 9.3.2.22. 222-E

E(B3LYP-D3/6-31+G(d)(THF)) =

-720,149176

E(LCCSD/6-311+G(d,p)(THF)) =

-717,672884

G(LCCSD/6-311+G(d,p)(THF)) =

-717,4203184

C1 -4.0283386761 1.2426466509  
2.2081876906

C2 -2.7003359388 1.2848377613  
1.7741280255

C3 -2.0382548792 0.1173762066  
1.3439768511

C4 -2.7535436685 -1.0987844381  
1.3567337686

C5 -4.0792747840 -1.1414329899  
1.7879196749

C6 -4.7231403956 0.0284948847  
2.2171607371

C7 -0.6376042275 0.2225156254  
0.9041101497

C8 0.1893511585 -0.7751277611  
0.5158822047

B9 1.6527039408 -0.5220699464  
0.0831279111

O10 2.2774796421  
0.7074702698 0.1177081790

C11 3.5451662615  
0.5719496588 -0.6053032832

C12 3.8291302449  
-0.9727372263 -0.4893448294

O13 2.4753830827  
-1.5264669985 -0.3871805467

C14 4.5209601845  
-1.5929517838 -1.6993930288

C15 3.2819587956  
1.0339477787 -2.0435018937

C16 4.5612244788

-1.3607823223 0.8012599476

C17 4.5852840350

1.4701108411 0.0575008626

H18 -4.5196286109

2.1557970832 2.5378988578

H19 -2.1649216962

2.2333171801 1.7686400307

H20 -2.2753472089

-2.0167468822 1.0242116589

H21 -4.6151976393

-2.0884424152 1.7888677851

H22 -5.7573844654

-0.0087803120 2.5529935351

H23 -0.2414058044

1.2403608803 0.9042995479

H24 -0.1758153615

-1.8034851427 0.5074116212

H25 5.5001287776

-1.1257050167 -1.8588743175

H26 4.6773756268

-2.6638090894 -1.5279491962

H27 3.9253094379

-1.4769941480 -2.6085873321

H28 4.2014557218

1.0190445360 -2.6385884844

H29 2.5356578223

0.4006666917 -2.5353717439

H30 2.8997931607

2.0601084877 -2.0234628971

H31 5.6053997863

-1.0304203180 0.7786491413

H32 4.0746881893

-0.9255922369 1.6810171635

H33 4.5465112152

-2.4511069340 0.9055782376

H34 5.5691053282

1.3171700824 -0.4023757637

H35 4.3051162903

2.5207974827 -0.0774635948

H36 4.6652460307  
1.2737231538 1.1299071213

#### 9.3.2.23. 223-Z

E(B3LYP-D3/6-31+G(d)(THF)) =  
-718,168534  
E(LCCSD/6-311+G(d,p)(THF)) =  
-716,102769  
G(LCCSD/6-311+G(d,p)(THF)) =  
-715,912716

C1 -4.0300243675 1.0638828581  
2.2867599342  
C2 -2.6849481805 0.9353361220  
1.9307448854  
C3 -2.1605829503 -0.3026860215  
1.5185247617  
C4 -3.0173661671 -1.4210573542  
1.5134315124  
C5 -4.3648034469 -1.2945118109  
1.8611200684  
C6 -4.8780110894 -0.0489173139  
2.2454916918  
C7 -0.7417061308 -0.4728715826  
1.1333853939  
C8 0.0272250698 0.3590107879  
0.3966775793  
Si9 -0.3513397140 1.9227387637  
-0.6030095540  
C10 0.8676254859  
1.8851275205 -2.0527189649  
C11 -2.1098208000  
1.9522735756 -1.3005114821  
C12 -0.0207113106  
3.4911731779 0.4113217505  
H13 -4.4139124076  
2.0311850042 2.6056355017  
H14 -2.0275742515  
1.7974390500 1.9942083983

H15 -2.6239966714  
-2.3935226054 1.2201728755  
H16 -5.0139544428  
-2.1677063709 1.8373385402  
H17 -5.9255200237  
0.0496970609 2.5233960131  
H18 -0.2992640741  
-1.4094552536 1.4871469583  
H19 1.0609436835  
0.0194136287 0.2647374924  
H20 0.7517700642  
2.7762915889 -2.6839393507  
H21 1.9059943398  
1.8562702694 -1.6963937997  
H22 0.7022105947  
1.0015970408 -2.6834021424  
H23 -2.1908875493  
2.7629657481 -2.0375459002  
H24 -2.3426590985  
1.0081889871 -1.8094755785  
H25 -2.8712144110  
2.1149471694 -0.5311095442  
H26 -0.1270762765  
4.3804735578 -0.2256952310  
H27 -0.7162970663  
3.5977921474 1.2532234348  
H28 0.9998285675  
3.4874130941 0.8164239806

#### 9.3.2.24. 223-E

E(B3LYP-D3/6-31+G(d)(THF)) =  
-718,174588  
E(LCCSD/6-311+G(d,p)(THF)) =  
-716,106671  
G(LCCSD/6-311+G(d,p)(THF)) =  
-715,917751

C1 -3.9066643656 0.7741172685  
2.8072315414

C2 -2.5283335997 0.6749811575  
 2.5949544040  
 C3 -2.0080720919 -0.0206561292  
 1.4852076106  
 C4 -2.9193734834 -0.6156333409  
 0.5887870719  
 C5 -4.2953700393 -0.5176336710  
 0.7984907426  
 C6 -4.7974699270 0.1772655092  
 1.9086436862  
 C7 -0.5421309262 -0.0891006631  
 1.3207435309  
 C8 0.1660936109 -0.7106109389  
 0.3535298787  
 Si9 2.0453234948 -0.7286483407  
 0.2477359222  
 C10 2.6499707664  
 -2.5227977417 0.3078286428  
 C11 2.5791326387  
 0.0447690767 -1.3968170663  
 C12 2.7824493649  
 0.2494962092 1.6896395548  
 H13 -4.2833432389  
 1.3163540720 3.6724045148  
 H14 -1.8417582830  
 1.1430896660 3.2993421044  
 H15 -2.5542546564  
 -1.1582522090 -0.2797763059  
 H16 -4.9815908440  
 -0.9838618197 0.0942254624  
 H17 -5.8710603825  
 0.2519852786 2.0690287836  
 H18 0.0054889074  
 0.4417118071 2.1028568545  
 H19 -0.3833741085  
 -1.2422671245 -0.4295014444  
 H20 3.7426855214  
 -2.5684318771 0.2055066195  
 H21 2.3764783452  
 -3.0014582563 1.2570859320

H22 2.2107010478  
 -3.1133314928 -0.5069400579  
 H23 3.6709106648  
 0.0026869445 -1.5099619559  
 H24 2.1322837395  
 -0.4883116519 -2.2463413694  
 H25 2.2708303743  
 1.0965342084 -1.4572086324  
 H26 3.8788486724  
 0.2378820481 1.6306198446  
 H27 2.4575316617  
 1.2979220032 1.6734689132  
 H28 2.4947896170  
 -0.1805614257 2.6578377740

### 9.3.2.25. BpinOLi

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -494,067786  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -492,255082  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -492,2261381

C1 -0.0319596422 -0.1102685995  
 0.1294293127  
 O2 0.0406572327 1.3181254410  
 -0.1201060555  
 B3 -0.9626551805 1.6968943705  
 -1.0723625474  
 O4 -1.5545947872 0.4917785353  
 -1.5738914353  
 C5 -0.7472632247 -0.6432782881  
 -1.1687384534  
 C6 0.2415767777 -0.9452538599  
 -2.3065016917  
 C7 1.3751601534 -0.6787933283  
 0.3481145833

C8 -0.8569954452 -0.3459683383  
 1.4054342614  
 C9 -1.6388282367 -1.8672224984  
 -0.9439760832  
 O10 -1.2791616312  
 2.9259091192 -1.4311320060  
 H11 0.8435683217  
 -1.8360167924 -2.0908437818  
 H12 -0.3217576493  
 -1.1292496847 -3.2279685985  
 H13 0.9179611171  
 -0.1011023646 -2.4777221653  
 H14 1.3373109412  
 -1.7748258799 0.4061236840  
 H15 2.0617452213  
 -0.3994692169 -0.4555056342  
 H16 1.7886380144  
 -0.3107591889 1.2946720670  
 H17 -0.8907482110  
 -1.4128409218 1.6591703719  
 H18 -0.3875223019  
 0.1840268945 2.2417996360  
 H19 -1.8841345984  
 0.0176028061 1.2974326766  
 H20 -1.0452100531  
 -2.7027443049 -0.5504035250  
 H21 -2.4518650982  
 -1.6610260156 -0.2425402578  
 H22 -2.0800146381  
 -2.1894270591 -1.8946433246  
 Li23 -1.9344545423  
 4.9539115441 -2.9342665208

### 9.3.2.26. TMSOLi

E(B3LYP-D3/6-31+G(d)(THF)) =  
 -492,089133  
 E(LCCSD/6-311+G(d,p)(THF)) =  
 -490,723782  
 G(LCCSD/6-311+G(d,p)(THF)) =  
 -490,7225325  
  
 C1 0.0630734024 0.0251585070  
 0.0027644189  
 Si2 1.9852426865 -0.0737498590  
 0.0216681163  
 C3 2.4289844851 0.9975708457  
 -1.5032932365  
 C4 2.3786580921 1.0650325522  
 1.5137623722  
 H5 -0.1919062194 1.0971706479  
 -0.0410491962  
 H6 -0.4071533816 -0.4468673554  
 -0.8699932641  
 H7 -0.4156542212 -0.3735665911  
 0.9076805924  
 H8 1.9965061145 2.0015585428  
 -1.3697510344  
 H9 3.5106948802 1.1213280164  
 -1.6444963003  
 H10 2.0084347760  
 0.5883190831 -2.4323688634  
 H11 1.9672176324  
 2.0652641147 1.3049301826  
 H12 1.9032046784  
 0.7124933406 2.4402045280  
 H13 3.4527762939  
 1.1857733827 1.7050535857  
 O14 2.7035713724  
 -1.5519956035 0.0500239981  
 Li15 4.3664768319  
 -2.8445498062 -0.1139034789





## 10. References

- [1] Yamatsugu, K.; Kanai, M. *Chem. Rev.* **2023**, *123*, 6793-6838.
- [2] Fischer, E.; Zach, K. *Sitzungsber. Kl. Preuss. Akad. Wiss.* **1913**, *27*, 311.
- [3] Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 5288-5290.
- [4] Poulsen, T. B. *Acc. Chem. Res.* **2021**, *54*, 1830-1842.
- [5] Cavallaro, C. L.; Schwartz J. *J. Org. Chem.* **1995**, *60*, 7055-7057.
- [6] Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X.; Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532-2547.
- [7] Herrmann, J. M.; König, B. *Eur. J. Org. Chem.* **2013**, *31*, 7017-7027.
- [8] Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770-1771.
- [9] Kinf, H. H. *Org. Biomol. Chem.* **2019**, *17*, 4153-4182.
- [10] Das, R.; Das, M.; Mukherjee, D.; Kundu, T. *Synthesis* **2024**, *56*, 1070-1096.
- [11] (a) Bennett, C. S.; Carmen Galan, M. *Chem. Rev.* **2018**, *118*, 7931-7985.  
(b) Marino, C.; Bordoni, A. V. *Org. Biomol. Chem.* **2022**, *20*, 934-962.
- [12] Gómez, A. M.; Lobo, F.; López, J. C. *Carbohydr. Chem.* **2016**, *41*, 26-58.
- [13] Zubkov, O. A.; Ferrier, R. J. *Org. React.* **2003**, *62*, 569-736.
- [14] Torabi, M.; Zolfigol, M. A.; Yarie, M.; Notash, B.; Azizian, S.; Azandaryani, M. M. *Sci. Rep.* **2021**, *11*, 16846.
- [15] Gómez, A. M.; Miranda, S.; López, J. C. *Carbohydr. Chem.* **2017**, *42*, 210-247.
- [16] Guo, Y.; Pei, C.; Koenigs R. M. *Chem. Cat. Chem.* **2020**, *12*, 4014-4018.
- [17] (a) Shinozuka, T. *ACS Omega* **2021**, *6*, 8447-8455. (b) Boucard, V., Larrieu, K., Lubin-Germain, N., Uziel, J.; Augé, J. *Synlett* **2003**, *2003*, 1834-1837. (c) Vaňková, K., Rahm, M., Choutka, J., Pohl, R.; Parkan, K. *Chem. Eur. J.* **2021**, *27*, 10583-10588. (d) Xiong, D.-C., Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709-1712.

- [18] (a) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797-1801. (b) Leidy, M. R., Mason Hoffman, J.; Pongdee, R. *Tetrahedron Lett.* **2013**, *54*, 6889-6891.
- [19] Kikuchi, T.; Takagi, J.; Isou, H.; Miyaura, N. *Chem. J.* **2008**, *3*, 2082-2090.
- [20] Pohl, R.; Kitora, M.; Parkan, K. *Chem. Eur. J.* **2014**, *20*, 4414-4419.
- [21] Choutka, J.; Pohl, R.; Parkan, K. *ACS Omega* **2018**, *3*, 7875-7887.
- [22] Chen, A.; Han, Y.; Wu, R.; Yang, B.; Zhu, L.; Zhu, F. *Nature Com.* **2024**, *15*, 5228.
- [23] Bischofberger, K.; Hall, R. H.; Jordan, A. J. *Chem. Soc., Chem. Commun.* **1975**, 806.
- [24] Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449.
- [25] Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395.
- [26] RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458.
- [27] Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406.
- [28] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.
- [29] Lakhrissi, Y.; Taillefumier, C.; Chrétien, F.; Chapleur, Y. *Tetrahedron Lett.* **2001**, *42*, 7265-7268.
- [30] Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1437.
- [31] Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 750-752.
- [32] Gueyrard, D.; Haddoub, R.; Salem, A.; Bacar, N. S.; Goekjian, P. G. *Synlett* **2005**, 520-522.
- [33] Gueyrard, D.; Fontaine, P.; Goekjian, P. G. *Synthesis* **2006**, 1499-1503.
- [34] Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747-749.

- [35] (a) Pfund, E.; Lequeux, T.; Gueyrard, D. *Synthesis* **2015**, 47, 1534-1546.  
 (b) Habib, S.; Larnaud, F.; Pfund, E.; Lequeux, T.; Fenet, B.; Goekjian, P. G.; Gueyrard, D. *Eur. J. Org. Chem.* **2013**, 2013, 4986.
- [36] Habib, S.; Gueyrard, D. *Eur. J. Org. Chem.* **2015**, 2015, 871-875.
- [37] (a) Oka, N.; Mori, A.; Suzuki, K.; Ando, K. *J. Org. Chem.* **2021**, 86, 657-673. (b) Oka, N.; Mori, A.; Suzuki, K.; Ando, K. *Eur. J. Org. Chem.* **2021**, 2021, 5922-5933.
- [38] de Pouilly, P.; Chénédé, A.; Mallet, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, 33, 8065-8068.
- [39] Taylor, R. J. K.; McAllister, G. D.; Franck, R. W. *Carbohydr. Res.* **2006**, 341, 1298-1311.
- [40] (a) Ramberg, L.; Bäcklund, B. *Ark. Kemi. Mineral. Geol.* **1940**, 27, 1-50 (*Chem. Abstr.* **1940**, 34, 4725). (b) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, 39, 8225-8228. (c) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. *Tetrahedron Lett.* **1998**, 39, 8179.
- [41] Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, 91, 7510-7512.
- [42] Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *Chem. Commun.* **1994**, 1771-1772.
- [43] Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 2002, 1323-1336.
- [44] Yang, W. B.; Chang, C. F.; Wang, S. H.; Teo, C. F.; Lin, C. H. *Tetrahedron Lett.* **2001**, 42, 4657-4660.
- [45] Yang, W. B.; Wu, C. Y.; Chang, C. C.; Wang, S. H.; Teo, C. F.; Lin, C. H. *Tetrahedron Lett.* **2001**, 42, 6907.
- [46] Yang, W. B.; Yang, Y. Y.; Gu, Y. F.; Wang, S. H.; Chang, C. C.; Lin, C. H. *J. Org. Chem.* **2002**, 67, 3773-3782.
- [47] Gomez, A. M.; Danelon, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002**, 2024-2025.

- [48] Thien, H.-T. T.; Novoa, A.; Pellegrini-Moise, N.; Chrétien, F.; Didierjean, C.; Chapleur, Y. *Eur. J. Org. Chem.* **2011**, *2011*, 6939-6951.
- [49] Bandzouzi, A.; Chapleur, Y. *Carbohydr. Res.* **1987**, *171*, 13-24.
- [50] Lakhriissi, Y.; Taillefumier, C.; Lakhriissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2000**, *9*, 417-421.
- [51] Chang, C. F.; Yang, W. B.; Chang, C. C.; Lin, C. H. *Tetrahedron Lett.* **2002**, *43*, 6515-6519.
- [52] Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283-4295.
- [53] Taillefumier, C.; Lakhriissi, Y.; Lakhriissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1707-1711.
- [54] Shin, Y.-H.; Beom, J. Y.; Chung, B.; Shin, Y.; Byun, W. S.; Moon, K.; Bae, M.; Lee, Q. K.; Oh, K.-B.; Shin, J.; Yoon, Y. J.; Oh, D.-C. *Org. Lett.* **2019**, *21*, 1804-1808.
- [55] Bernd, M.; Christoph, S.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2893-2897.
- [56] Dumitrescu, L.; Eppe, G.; Tikad, A.; Pan, W.; Bkassiny, S. E.; Gurcha, S. S.; Ardá, A.; Jiménez-Barbero, J.; Besra, G. S.; Vincent, S. P. *Chem. Eur. J.* **2014**, *20*, 15208-15215.
- [57] Habib, S.; Larnaud, F.; Pfund, E.; Mena Barragan, T.; Lequeux, T.; Ortiz Mellet, C.; Goekjian, P. G.; Gueyrard, D. *Org. Biomol. Chem.* **2014**, *12*, 690-699.
- [58] Frédéric, C. J.-M.; Vincent, S. *Tetrahedron* **2018**, *74*, 6512-6519.
- [59] Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494.
- [60] Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.
- [61] Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890-931.
- [62] Geier, S. J.; Vogels, C. M.; Melanson, J. A.; Westcott, S. A. *Chem. Soc. Rev.* **2022**, *51*, 8877-8922.

- [63] Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177-2250.
- [64] (a) Matteson, D. S. *J. Org. Chem.* **2013**, *78*, 10009-10023. (b) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398-4403.
- [65] Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583-586.
- [66] Lam, P.; Clark, C.; Saubern, S.; Adams, J.; Winters, M.; Chan, D.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.
- [67] Barth, R. F.; Vicente, M. H.; Harling, O. K.; Kiger III, W. S.; Riley, K. J.; Binns, P. J.; Wagner, F. M.; Suzuki, M.; Aihara, T.; Kato, I.; Kawabata, S. *Radiat Oncol* **2012**, *7*, 146.
- [68] Matsumoto, A.; Kuwata, H.; Kimura, S.; Matsumoto, H.; Ochi, K.; Morooka, Y.; Watanabe, A.; Yamada, H.; Ishii, H.; Miyazawa, T.; Chen, S.; Baba, T.; Yoshida, H.; Nakamura, T.; Inoue, H.; Ogawa, Y.; Tanaka, M.; Miyahara, Y.; Suganami, T. *Commun Biol* **2020**, *3*, 313.
- [69] Grams, R. J.; Santos, W. L.; Scorei, I. R.; Abad-García, A.; Rosenblum, C. A.; Bitá, A.; Cerecetto, H.; Viñas, C.; Soriano-Ursúa, M. A. *Chem. Rev.* **2024**, *124*, 2441-2511.
- [70] Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.-T.; Plamondon, L.; Stein, R. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333-338.
- [71] Hušák, M.; Jegorov, A.; Rohlíček, J.; Fitch, A.; Czernek, J.; Kobera, L.; Brus, J. *Cryst. Growth Des.* **2018**, *18*, 3616-3625.
- [72] Bush, K. *ACS Infect. Dis.* **2018**, *4*, 84-87.
- [73] Carreras, J.; Caballero, A.; Pérez, P. J. *Chem. Asian J.* **2019**, *14*, 329-343.
- [74] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
- [75] Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695.
- [76] H. C. Brown, *Hydroboration*, Wiley Interscience, New York, **1962**.
- [77] Woods, W. G. *J. Org. Chem.* **1966**, *31*, 2766-2768.

- [78] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249-5255.
- [79] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482-3485.
- [80] Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392-1395.
- [81] a) Arase, A.; Hoshi, M.; Mijin A.; Nishi, K. *Synth. Commun.* **1995**, *25*, 1957-1962. b) Shirakawa, K.; Arase, A.; Hoshi, M. *Synthesis*, **2004**, 1814-1820.
- [82] Ho, H. E.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**, *16*, 4670-4673.
- [83] Wen, K.; Chen, J.; Gao, F.; Bhadury, P. S.; Fan, E.; Sun, Z. *Org. Biomol. Chem.* **2013**, *11*, 6350-6356.
- [84] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127-3128.
- [85] Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283-3286.
- [86] (a) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990-4991. (b) Cid, J.; Carbó, J. J.; Fernández, E. *Chem. Eur. J.* **2012**, *18*, 1512-1521.
- [87] Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982-983.
- [88] (a) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, 2943-2945. (b) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733-734.
- [89] Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179-4184.
- [90] Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358-6359.
- [91] Suginome, M.; Yamamoto, A.; Murakami, M. *J. Organomet. Chem.* **2005**, *690*, 5300-5308.
- [92] Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3475-3479.

- [93] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510.
- [94] Murata, M.; Watanabe S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458-6459.
- [95] Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 126-127.
- [96] Takagi, J.; Kamon, A.; Ishiyama, T.; Miyaura, N. *Synlett.* **2002**, *11*, 1880-1882.
- [97] Qiu, X.; Li, Y.; Zhou, L.; Chen, P.; Li, F.; Zhang, Y.; Ling, Y. *Org. Lett.* **2020**, *22*, 6424-6428.
- [98] Selander, N.; Willy, B.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4051-4053.
- [99] Takaya, J.; Kirai, N.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 12980-12983.
- [100] (a) Brumsted, C. J.; Moorlag, H.; Radinov, R. N.; Ren, Y.; Waldmeier, P. WO2012010538. (b) Kincaid, J.; Duncton, M. WO2020106308.
- [101] (a) Tran, M.-K.; Ready, J. M. *Angew. Chem. Int. Ed.* **2024**, *63*, e202407824. (b) Schütz, R.; Schmidt, S.; Bracher, F. *Tetrahedron* **2020**, *76*, 131150-131158. (c) Niu, Y.; Zhang, H.; Li, Z.; Xie, X.; Liu, Y. *Org. Lett.* **2024**, *26*, 6921-6926.
- [102] Kondoh, A.; Jamison, T. F. *Chem. Commun.* **2010**, *46*, 907-909.
- [103] Morimoto, M.; Miura, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 12659-12663.
- [104] (a) Sasaki, I.; Doi, H.; Hashimoto, T.; Kikuchi, T.; Ito, H.; Ishiyama, T. *Chem. Commun.* **2013**, *49*, 7546-7548. (b) Wang, C.; Wu, C.; Ge, S. *ACS Catal.* **2016**, *6*, 7585-7589. c) Basappa, S.; Prakash, A.; Talekar, S. S.; Mane, M. V.; Bose, S. K. *ACS Catal.* **2024**, *14*, 3065-3073.
- [105] (a) Daini, M.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 4758-4761. (b) Daini, M.; Suginome, M. *Chem. Commun.* **2008**, 5224-5226.

- [106] McAtee, J. R.; Martin, S. E.; Ahneman, D. T.; Johnson, K. A.; Watson, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3663-3667.
- [107] Reid, W. B.; Spillane, J. J.; Krause, S. B.; Watson, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 5539-5542.
- [108] Reid, W. B.; Watson, D. A. *Org. Lett.* **2018**, *20*, 6832-6835.
- [109] Idowu, O. O.; Hayes, J. C.; Reid, W. B.; Watson, D. A. *Org. Lett.* **2021**, *23*, 4838-4842.
- [110] Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58-71.
- [111] Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031-6034.
- [112] Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130-3138.
- [113] Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733-7736.
- [114] Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R. Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026-6029.
- [115] (a) Marciniak, B.; Jankowska, M.; Pietraszuk, C. *Chem. Commun.* **2005**, 663-665. (b) Oosting, P.; Thomas, E.; Pamuk, R.; Folleas, B.; Brayer, J.-L.; De Carne Carnavalet B.; Meyer, C.; Cossy, J. US2015329566.
- [116] Cainelli, G.; Dal Bello, G.; Zubiani, G. *Tetrahedron Lett.* **1966**, *36*, 4315-4318.
- [117] Castle, R. B.; D. S. Matteson, D. S. *J. Organomet. Chem.* **1969**, *20*, 19-28.
- [118] Matteson, D. S.; Tripathy, P. B. *J. Organomet. Chem.* **1974**, *69*, 53-62.
- [119] Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94*, 6854-6856.
- [120] Matteson, D. S.; Moody, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 3196-3197.
- [121] Cuenca, A. B.; Fernández, E. *Chem. Soc. Rev.* **2021**, *50*, 72-86.
- [122] Endo, K.; Hirokami, M.; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469-3472.



- [123] Mukaiyama, T.; Murakami, M.; Oriyama, T.; Yamaguchi, M. *Chem. Lett.* **1981**, 10, 1193-1196.
- [124] Iacono, C. E.; Stephens, T. C.; Rajan T. S.; Pattison, G. A. *J. Am. Chem. Soc.* **2018**, 140, 2036-2040.
- [125] Wang, T.; Kohrt, S.; Daniliuc, C. G.; Kehr, G.; Erker, G. *Org. Biomol. Chem.* **2017**, 15, 6223-6232.
- [126] Zheng, P.; Zhai, Y.; Zhao, X.; Xu, T. *Chem. Commun.* **2018**, 54, 13375-13378.
- [127] Sun, W.; Wang, L.; Hu, Y.; Wu, X.; Xia, C.; Liu, C. *Nat. Commun.* **2020**, 11, 3113-3124.
- [128] Korch, K. M.; Watson, D. A. *Chem. Rev.* **2019**, 119, 8192-8228.
- [129] Regier, J.; Ghanty, S.; Bolshan Y. *J. Org. Chem.* **2022**, 87, 524-530.
- [130] (a) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Prep. Proced. Int.* **1995**, 27, 707-709. (b) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, 79, 19.
- [131] Frédéric, C. J.-M.; Cornil, J.; Vandamme, M.; Dumitrescu, L.; Tikad, A.; Robiette, R.; Vincent, S. P. *Org. Lett.* **2018**, 20, 6769-6773.
- [132] (a) Bagherzadeh, S.; Mankad, N. P. *J. Am. Chem. Soc.* **2015**, 137, 10898-10901. (b) Ji, P.; Sawano, T.; Lin, Z.; Urban, A.; Boures, D.; Lin, W. *J. Am. Chem. Soc.* **2016**, 138, 14860-14863.
- [133] (a) Nallagonda, R.; Padala, K.; Masarwa, A. *Org. Biomol. Chem.* **2018**, 16, 1050-1064; (b) Wu, C.; Wang, J. *Tetrahedron Lett.* 2018, 59, 2128-2140.
- [134] Ali, H. A.; Goldberg, I.; Srebnik, M. *Organometallics*, **2001** 20, 3962-3965.
- [135] Wommack, A. J.; Kingsbury, J. S. *Tetrahedron Lett.* **2014**, 55, 3163-3166.
- [136] Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang Y.; Wang, J. *Org. Lett.* **2014**, 16, 448-451.
- [137] Ito, H.; Kubota, K. *Org. Lett.* **2012**, 14, 890-893.

- [138] Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. *Org. Lett.* **2014**, *16*, 6342-6345.
- [139] Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176-6179.
- [140] Hitosugi, S.; Tanimoto, D.; Nakanishi, W.; Isobe, H. *Chem. Lett.* **2012**, *41*, 972-973.
- [141] Kovalenko, M.; Yarmoliuk, D. V.; Serhiichuk, D.; Chernenko, D.; Smyrnov, V.; Breslavskiy, A.; Hryshchuk, O. V.; Kleban, I.; Rassukana, Y.; Tymtsunik, A. V.; Tolmachev, A. A.; Kuchkovska, Y. O.; Grygorenko, O. O. *Eur. J. Org. Chem.* **2019**, *33*, 5624-5635.
- [142] (a) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20-28. (b) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241-3267.
- [143] Lin, S.; Wang, L.; Aminoleslami, N.; Lao, Y.; Yagel, C.; Sharma, A. *Chem. Sci.* **2019**, *10*, 4684-4691.
- [144] Gawande, M. B.; Shelke, S. N.; Zboril, R.; S. Varma, R. S. *Acc. Chem. Res.* **2014**, *47*, 4, 1338-1348.
- [145] Kumar, N.; Reddy, R. R.; Masarwa, A. *Chem. Eur. J.* **2019**, *25*, 8008-8012.
- [146] Lenox, J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 1-5.
- [147] Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R.; *J. Org. Chem.* **1995**, *60*, 3020-3027.
- [148] Kim, B. J.; Matteson, D. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3056- 3058.
- [149] (a) Msayib, K. J., Watt, C. I. F. *Chem. Soc. Rev.*, **1992**, *21*, 237-243. (b) Mehrotra, R. C. *J. Non-Cryst. Solids* **1988**, *100*, 1-15. (c) Duffy, J. L.; Kuth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259-1260.
- [150] Tortajada, A.; Anderson, D. E.; Hevia, E. *Helv. Chim. Acta* **2022**, *105*, e202200060.
- [151] (a) Bole, L. J.; Tortajada, A.; Hevia, E. *Angew. Chem.* **2022**, *134*, e202204262. (b) Clanton, N. A.; Wilson, N. A.; Ortiz, E.; Blumberg, S. T.; Doug E. Frantz, D. E. *Org. Lett.* **2023**, *25*, 277–281.

- [152] Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295-297.
- [153] Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961.
- [154] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.
- [155] (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *105*, 1080-1106. (b) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, *10*, 1205-1222. (c) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, *18*, 3117-3125.
- [156] Yamada, K.; Fukuyama, T.; Fujii, S.; Raveli, D.; Fagnoni, M.; Ryu, I. *Chem. Eur. J.* **2017**, *23*, 8615-8618.
- [157] de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A.; Piccialli, G. *J. Org. Chem.* **2000**, *65*, 3432-3442.
- [158] Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. *Synlett* **2018**, *29*, 1749-1752.
- [159] Endo, K.; Kurosawa, F.; Ukaji, Y. *Chem. Lett.* **2013**, *42*, 1363-365.
- [160] Buss, D.; Colclough, E.; Pelter, A. *J. Chem. Soc., Chem. Commun.* **1987**, 297-299.
- [161] Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780-784.
- [162] D. J. Ager, *Organic Reactions, Volume 38*, Wiley Interscience, **1991**.
- [163] Bassindale, A. R.; Ellis, R. J.; Taylor, P. G. *Tetrahedron Lett.* **1984**, *25*, 2705-2708.
- [164] Raadt, A.; Stiitz, A. E. *Carbohydr. Res.* **1991**, *220*, 101-115.
- [165] Glänzer, B. I.; Csuk, R. *Carbohydr. Res.* **1991**, *220*, 79-92.
- [166] Mlynarski, J.; Banaszek, A. *Tetrahedron* **1999**, *55*, 2785-2794.
- [167] Matteson, D. S.; Majumdar, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 39-40.
- [168] Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230-236.
- [169] Brook, A. G.; MacRae, D. M.; Limburg, W. W. *J. Am. Chem. Soc.* **1967**, *89*, 5493-5495.

- [170] La Cascia, E.; Cuenca, A. B.; Fernández, E. *Chem. Eur. J.* **2016**, *22*, 18737-18741.
- [171] Snyder, H. R.; Konecky, M. S.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 3611.
- [172] Stephens, T. C.; Pattison, G. *Org. Lett.* **2017**, *19*, 3498-3501.
- [173] Fordham, J. M.; Grayson, M. N.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 15268-15272.
- [174] Hertz, V. H.; Massoth, J. G.; Bolte, M.; Lerner, H.-W.; Wagner, M. *Chem. Eur. J.* **2016**, *22*, 13181-13188.
- [175] Kumar, N.; Reddy, R. R.; Masarwa, A. *Chem. Eur. J.* **2019**, *25*, 8008-8012.
- [176] Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099-9103.
- [177] Lozada, J.; Xuan Lin, W.; Cao-Shen, R. M.; Astoria Tai, R.; Perrin, D. *Angew. Chem. Int. Ed.* **2023**, *62*, e202215371.
- [178] <https://chemazone.com/info?ID=151.722.906>, consulted 09/11/2024 for 2-(propan-2-yloxy)-2H-1,3,2-benzodioxaborole, CAS number 61676-63-9.
- [179] Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, *9*, 631-632.
- [180] Grenz, D. C.; Rose, D.; Wössner, J. S.; Wilbuer, J.; Adler, F.; Hermann, M.; Chan, C.-Y.; Adachi, C.; Esser, B. *Chem. Eur. J.* **2022**, *28*, e202104150.
- [181] Xiao, P.; Cao, Y.; Gui, Y.; Gao, L.; Song, Z. *Angew. Chem. Int. Ed.* **2018**, *57*, 4769-4773.
- [182] X.-F. Wu, *Solvents as Reagents in Organic Synthesis: Reactions and Applications*, Wiley-VCH, **2017**.
- [183] Kobayashi, T.; Pannell, K. H. *Organometallics* **1991**, *10*, 1960-1964.
- [184] Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835-838.
- [185] Hu, C.; He, J.-G.; O'Brien, D. H.; Irgolic, K. J. *J. Organomet. Chem.* **1984**, *268*, 31-38.

- [186] Brondani, D. J.; Corriu, R. J. P.; El Ayoubi, S.; Moreau, J. J. E.; Wong Chi Man, M. *Tetrahedron Letters* **1993**, *34*, 2111-2114.
- [187] Davison, N.; McMullin, C. L.; Zhang, L.; Hu, S.-X.; Waddell, P. G.; Wills, C.; Dixon, C.; Lu, E. *J. Am. Chem. Soc.* **2023**, *145*, 6562-6576.
- [188] Zaleski, C.M. *Advances in Metallocrown Chemistry*, Springer, Cham., **2022**.
- [189] Al-Aziz, A.; Srebnik, M. *Synth. Commun.* **2002**, *32*, 2575-2579.
- [190] Tappin, N. D. C.; Renaud, P. *Adv. Synth. Catal.* **2021**, *363*, 275-282.
- [191] Murai, N.; Yonaga, M.; Tanaka, K. *Org. Lett.* **2012**, *14*, 1278-1281.
- [192] Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2031-2034.
- [193] Williams, D. B. G.; Shaw, M. L.; Green, M. J.; Holzapfe, C. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 560-563.
- [194] Tolstikova, L. L.; Belskikh, A. V.; Shainyan, B. A. *Russ. J. Gen. Chem.* **2011**, *81*, 474-480.
- [195] Fukuda, N.; Ikemoto, T. *J. Org. Chem.* **2010**, *75*, 4629-4631.
- [196] Sakaine, G.; Leitis, Z.; Locmele, R. ; Smits, G. *Eur J Org Chem* **2022**, *26*, e202201217.
- [197] Pospíšil, J.; Robiette, R.; Sato, H.; Debrus, K. *Org. Biomol. Chem.* **2012**, *10*, 1225.
- [198] Fleige, M.; Mobus, J.; vom Stein, T.; Glorius, F.; Stephan, D. W. *Chem. Commun.* **2016**, *52*, 10830-10833.
- [199] Molloy, J. J.; Law, R. P.; Fyfe, J. W. B.; Seath, C. P.; Hirst, D. J.; Watson, A. J. B. *Org. Biomol. Chem.* **2015**, *13*, 3093-3102.
- [200] Walton, J. C.; McCarroll, A. J.; Qiao Chen, Q.; Carboni, B.; Nziengui, R. *J. Am. Chem. Soc.* **2000**, *122*, 5455-5463.
- [201] Romeo, J. R.; Lucera, J. D.; Jensen, D.; Davis, L. M.; Bennett, C. S. *Org. Lett.* **2023**, *25*, 3760-3765.
- [202] Tótha, M.; Somsák, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 942-943.

- [203] Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534-5539.
- [204] Qiu, X.; Li, Y.; Zhou, L.; Chen, P.; Li, F.; Zhang, Y.; Ling, Y. *Org. Lett.* **2020**, *22*, 6424-6428.
- [205] Lyu, Y.; Toriumi, N.; Iwasawa, N. *Org. Lett.* **2021**, *23*, 9262-9266.
- [206] Dominguez-Molano, P.; Bru, G.; Salvado, O.; Maza, R. J.; Cárbo, J. J.; Fernández, E. *Chem. Commun.* **2021**, *57*, 13361-13364.
- [207] Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J.-I. *Org. Lett.* **2004**, *6*, 4093-4096.
- [209] Brégent, T.; Bouillon, J.-P.; Poisson, T. *Chem. Eur. J.* **2021**, *27*, 13966-13970.
- [208] Li, J.-J.; Wang, C.-G.; Yu, J.-F.; Wang, P.; Yu, J.-Q. *Org. Lett.* **2020**, *22*, 4692-4696.
- [210] Jaguar 8.5, Schrodinger, Inc., New York, NY, **2014**.
- [211] a) Becke, A. D. *Chem. Phys.* **1993**, *98*, 5648-5652. b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.
- [212] Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.
- [213] Bon, D. J.-Y. D.; Chrenko, D.; Kováč, O.; Ferugová, V.; Lasák, P.; Fuksová, M.; Zálešák, F.; Pospíšil, J. *Adv. Synth. Catal.* **2024**, *366*, 480-487.