Synthesis of Vinyl Boronates from Aldehydes and Ketones by Peterson Olefination: Investigation of the Peterson/Boron-Wittig Chemoselectivity

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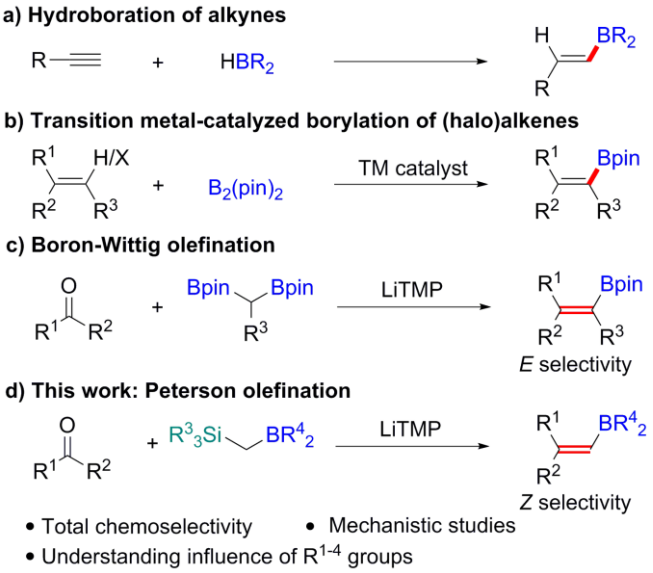
Abstract: We report our results on the development of the Peterson olefination using *gem*-borylsilylmethane derivatives to synthesize di- and tri-substituted vinyl boronates. We show that the electronic properties of the carbonyl partner have no effect on the Peterson/boron-Wittig chemoselectivity whereas the nature of the silane group plays an important role. A DFT study helps explain observed reactivity, chemoselectivity and stereoseletivity

Introduction

Vinyl boronates have attracted significant attention in organic chemistry for their pivotal role as versatile intermediates in a variety of synthetic transformations,[1-2] including the Suzuki-Miyaura coupling reaction.[3] Over the years, numerous methods have been developed for their synthesis (Scheme 1). Traditional approaches include the hydroboration of alkynes[4-6] and the transition metal-catalyzed borylation of (halo)alkenes.[7-10] A particularly noteworthy method is the boron-Wittig olefination of carbonyl compounds using *gem*-diborylalkanes.[11-13]

Scheme 1. Strategies for the synthesis of vinyl boronates.

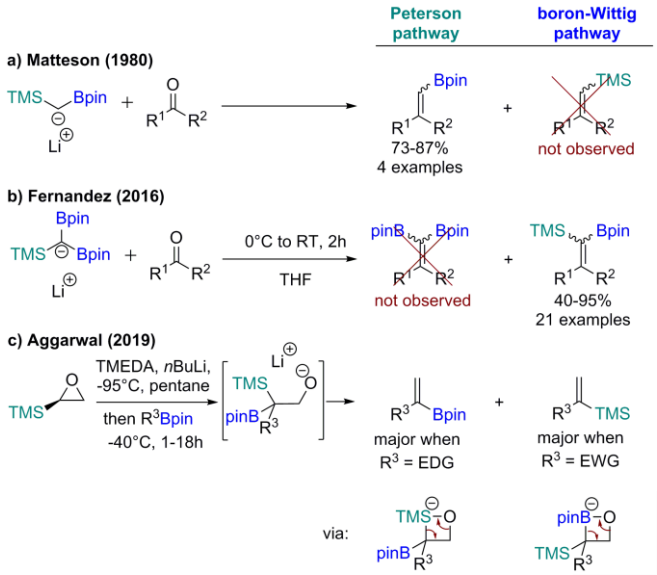


Despite the success of the boron-Wittig reaction, the exploration of alternative olefination strategies remains a compelling area of research. We sought that one alternative could be the Peterson olefination, a reaction well-known for the synthesis of alkenes via the reaction of α-silyl carbanions with carbonyl compounds (see Scheme 1d).[14-15] However, a critical challenge in this endeavour is chemoselectivity. Specifically, it is crucial to discern whether the reaction would favor the Peterson olefination pathway over the boron-Wittig pathway and identify the factors determining this chemoselectivity.

In 1980, Matteson showed on four examples that the reaction of lithio(trimethylsilyl)methaneboronate with carbonyl compounds leads exclusively to the formation of the corresponding pinacol vinylboronates (Scheme 2a).[16] More recently, Fernandez *et al.* reported the reaction of $HC(Bpin)_2(SiMe_3)$ with various ketones.[17-18] In these cases, 1-boryl-1-sylilalkenes are obtained via a boron-Wittig olefination, with no trace of the Peterson reaction product, *i.e.* a *gem*-diborylalkene (Scheme 2b). In the course of the development of a vinylidene homologation of boronic esters strategy, Aggarwal *et al.* investigated the selectivity between B-O and Si-O elimination pathways (Scheme 2c).[19] They found that

derivatives bearing an aliphatic or an electron-rich aryl substituent (R^3) provide vinylidene boronic esters, via Si-O elimination (Peterson pathway), while electron-deficient substituents favor the B-O elimination (boron-Wittig pathway).

Scheme 2. Peterson/boron-Wittig chemoselectivity.



These studies show that substitution of the central carbon atom of the boron-silicon reactant has a strong influence on Peterson/boron-Wittig chemoselectivity. However, the impact of the nature of the carbonyl partner has not yet been studied nor the effect of boron and silicon substituents.

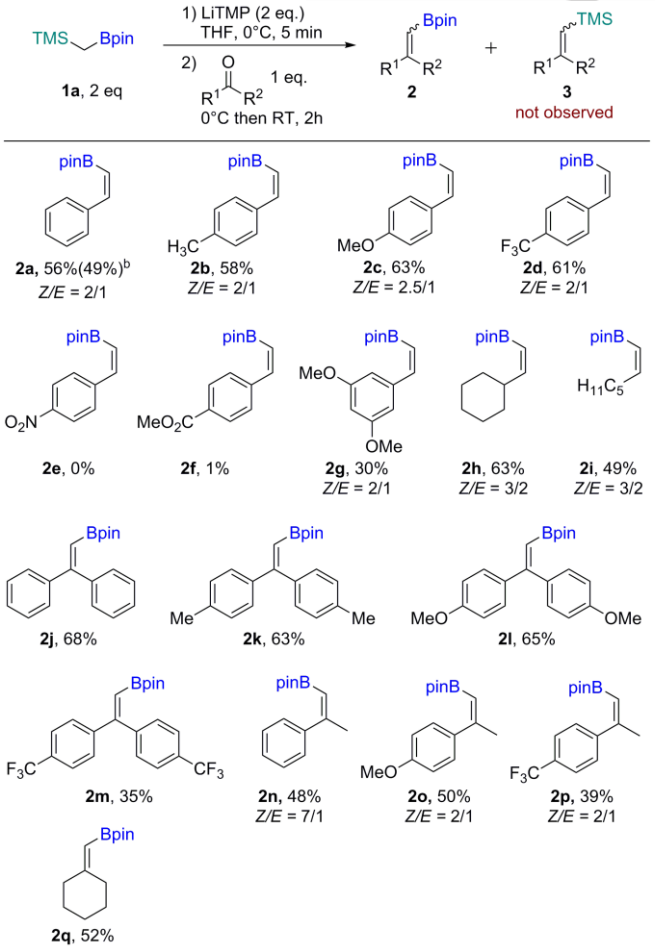
Herein, we describe our study on the development of the Peterson reaction for the synthesis vinyl boronates. We show that the Peterson pathway is consistently preferred over the boron-Wittig reaction regardless of the nature of the carbonyl partner. However, the electronic properties of the silane group are found to play an important role. The developed method enables the *Z*-stereoselective synthesis of di- and tri-substituted vinyl boronates. A computational study provides insights into factors determining reactivity, Peterson/boron Wittig selectivity and stereoselectivity.

Results and Discussion

Our work began with the optimization of the olefination process using benzaldehyde and *gem*-borylsilylmethane **1a** as reference substrates (see SI for full optimization data). First, we note that the use of a hindered lithium base such as lithium 2,2,6,6-tetramethylpiperidine (LiTMP) enables avoiding the deborylation of **1a**, as reported by Matteson.[16] Interestingly, whatever the reaction conditions, the silylated olefin **3a** was never observed, the reaction showing a total chemoselectivity in favor of the Peterson pathway.

Having established optimal reaction conditions, we explored the influence of the electronic properties of the aldehyde on chemo- and stereo-selectivities (Scheme 3).[20] With all the tested aldehydes, only the vinyl boronate **2** was obtained as the product, indicating a total chemoselectivity for the Peterson olefination pathway. A low *Z* stereoselectivity is observed regardless of the nature of the aldehyde. This is interesting since the boron-Wittig strategy provides preferentially *E* vinyl boronates. Notably, aromatic but also enolizable aliphatic aldehydes could be employed (see **2h** and **2i**). However, one limitation is the use of aromatic aldehydes bearing a strong mesomeric electron-withdrawing substituent which leads to a complete failure of the reaction (see **2e,f**).

Scheme 3: Olefination of aldehydes and ketones using **1a**.[a]



[a] Yield determined on the crude mixture by ^{1}H NMR using an internal standard.
[b] In brackets, yield in pure isolated product.

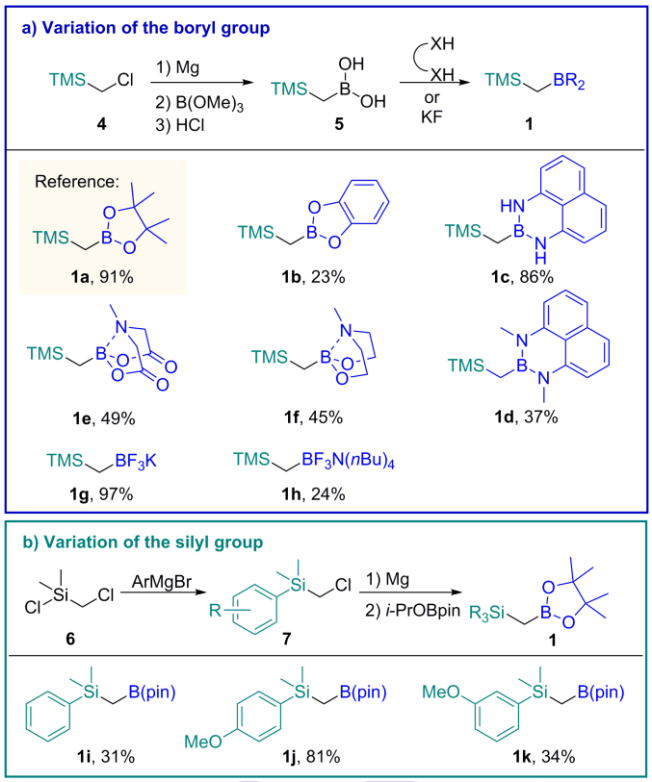
The borylating olefination is also efficient on (enolizable) ketones producing tri-substituted vinyl boronates with complete chemoselectivity. However, as for aldehydes, a decrease in yield is observed with substitution by electron-withdrawing groups, suggesting that electrophilicity of the carbonyl substrate is not determining for the overall reactivity. Interestingly, the preference of the *Z* isomer is preserved in the case of non-symmetric ketones (see **2n-p**). The higher *Z/E* selectivity observed for **2n** 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.

Thus, in contrast to the substitution at the BCSi carbon,[19] the nature of the carbonyl partner has no impact on the Peterson/boron-Wittig selectivity, with the exclusive Peterson olefination pathway being observed in all cases. On the other

hand, carbonyl substituents have an influence on reactivity. This effect is however counterintuitive since strong electron-withdrawing substituents, which increase electrophilicity of the carbonyl substrate, disfavor the reaction.

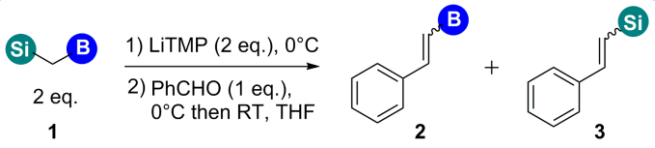
We next proceeded to investigate the influence of the nature of both the boryl and silyl groups. To achieve this, we synthesized a series of *gem*-borylsilylmethane substrates exhibiting different steric and electronic properties (Scheme 4). Derivatives **1b-h** were obtained from corresponding boronic acid (**5**) whereas the variation of the silyl group was enabled by the addition of a Grignard reagent onto the chloro(chloromethyl)dimethylsilane **6** followed by the installation of the Bpin group.

Scheme 4: Synthesis of *gem*-borylsilylmethane substrates (see SI for details).



Concerning the modification of the boryl group, none of the synthesized substrates (**1b-h**) led to the formation of an olefin, Bpin proved to be the only boryl group enabling the olefination. In the case of the catecholboronate group (**1b**) only traces of the vinyl boronate could be observed (Table 1, entry 2), probably due to the instability of **1b**. With Bdan (**1c**) and Bmida (**1e**) derivatives, the starting materials were fully recovered (entry 3). We attributed this to the acidity of the amine function and the protons α to the carbonyl groups, respectively, which compete with deprotonation of the central methylene group. Accordingly, we switched to their analogues without acidic protons, Bmdan (**1d**) and BMDEA (**1f**) derivatives, but no olefination product could be observed (entry 3). Instead, the boronic acid **5** was obtained after work up, hinting at a possible hydrolysis. The potassium trifluoroborate substrate **1g** proved to be insoluble in all the solvents compatible with our reaction conditions. Thus, we prepared the corresponding ammonium salt (**1h**), what allowed us to carry out the reaction in dichloromethane. However, again, only the starting materials were recovered. It is likely that the acidity of the central methylene group is too low to be deprotonated by LiTMP.

Table 1: Variation of the boryl and silyl groups.[a]



Entry	Substrate	2-*Z*	2-*E*	3-*E*
1	**1a**	36%	20%	0%
2	**1b**	traces	0%	0%
3	**1c-h**	0%	0%	0%
4	**1i**	9%	5%	traces
5	**1j**	13%	7%	2%
6	**1k**	39%	20%	5%

[a] Yield determined on the crude mixture by ^{1}H NMR using an internal standard.

We then turned our attention to the variation of the silyl group using dimethylarylsilyl derivatives (**1i-k**) with different electronic properties. In all cases, the borylated olefin was obtained as the main product, in a *Z*/*E* ratio of *ca.* 2:1 (entries 4-6, Table 1). The replacement of one methyl group by a phenyl (compare entries 1 and 4) leads however to a reduced yield, presumably due to the increased steric hindrance which disfavors the Peterson olefination. The *meta*-methoxy substitution of the aryl (**1k**, entry 6) shows that this effect can be compensated by increasing the electrophilicity of the silyl group. The deactivation of the Peterson pathway by steric effects is probably also why one observes, for the first time, traces of the silylated olefin (**3**), resulting from a boron-Wittig reaction. Though, electronic effects induced by aryl substitution have no significant impact on the Peterson/boron-Wittig chemoselectivity.

In order to gain insight into the origin of the high Peterson/boron-Wittig selectivity and the factors that determine stereoselectivity, DFT calculations were performed.[21] Investigation of the mechanism of the reaction between our reference substrates, **1a** and benzaldehyde, indicated that both the Peterson and the boron-Wittig pathways involve three steps, corroborating the postulated mechanisms for these transformations (Figure 1).[17,22-25] The first step, addition, is common to both processes. It can lead to two diastereomeric adducts but our calculations predict that the most favored pathway goes through **Adduct-*RS*** (see SI for full data). Next, **Adduct-*RS*** can cyclize toward either **BOcycle-*trans*** or **SiOcycle-*cis***. Both of these intermediates can then undergo elimination to produce a vinyl silane (**2a-*Z***) or a vinyl boronate (**3a-*E***), respectively.

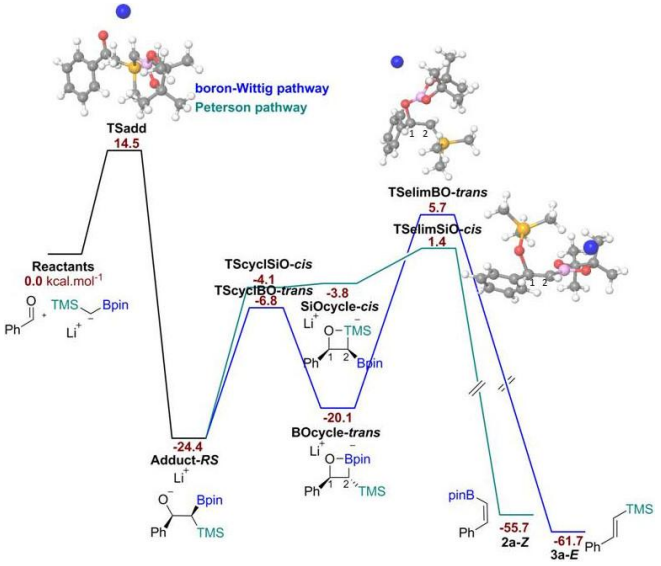


Figure 1. Mechanism for the competing Peterson and boron-Wittig olefinations. Relative free energies in kcal.mol^{-1}.

The analysis of the free energy profile shows that, in both pathways, the rate-determining transition state is the last step of the mechanism, the elimination to olefin (Scheme 5). This means that it is this latter step that governs chemoselectivity. Accordingly, our calculations predict a total chemoselectivity in favor of the Peterson pathway, **TSelimSiO-*cis*** lying 4.3 kcal.mol^{-1} lower than **TSelimBO-*trans*,** in good agreement with experiment. Indeed, ring-closure through B-O bond formation is more favored than via Si-O bond formation but elimination from **SiOcycle-*cis*** is highly favored as compared to elimination from **BOcycle-*trans***, resulting in a faster ring closure-elimination sequence in the case of the Peterson pathway. This easier elimination from **SiOcycle-*cis*** can be accounted for by the better stabilization of the developing negative charge on the α-carbon (C2) by the electron deficient boronate group in **TSelimSiO-*cis*** as compared to the silane group in **TSelimBO-*trans***, as shown by Aggarwal's studies.[19] Indeed, bystander substituents on C2 have a large impact on the TS stabilization due to the highly asynchronous nature of the transition state with an advanced C-Si or C-B bond breaking (see Figure 1). The highly asynchronous elimination TS explains also why, on the contrary, chemoselectivity remains unaffected by the substitution pattern at the carbonyl carbon (C1), as the C-O bond is barely broken in the transition state.

These computational findings provide a clear mechanistic rationale for the experimentally observed total chemoselectivity. The predicted energy difference between the elimination transition states (**TSelimSiO-*cis*** vs. **TSelimBO-*trans***) aligns well with the exclusive formation of the Peterson product, reinforcing that the nature of the elimination step dictates the overall pathway preference. Moreover, the computational analysis explains why the electronic properties of the carbonyl partner do not alter the Peterson/boron-Wittig selectivity.

The free energy profile also explains why the reactivity is not governed by the electrophilicity of the aldehyde. Indeed, addition of the *gem*-borylsilyl carbanion to the aldehyde is not the rate-determining step, which is instead the elimination step.

Conclusion

In summary, we have developed a Peterson olefination reaction using *gem*-borylsilylmethane derivatives with aldehydes and ketones, providing access to di- and tri-substituted vinyl boronic esters. The reaction proceeds with a consistent *Z*-stereoselectivity, whereas reported olefination methods provide preferentially *E*-vinyl boronates, and exhibits complete chemoselectivity in favor of the Peterson pathway. We show that the nature the carbonyl partner does not affect chemoselectivity, whereas the properties of the silyl group play an important role. Computational studies have revealed that elimination is the rate and chemoselectivity determining step whereas stereoselectivity is determined at the initial addition step.

Supporting Information

The authors have cited additional references within the Supporting Information.[26-43] The supporting information contains experimental procedures, characterization data and copies of NMR spectra for all new compounds, additional experimental observations and data, and computational details.

Acknowledgements

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Keywords: Boron-Wittig • Chemoselectivity • Density functional calculations • Peterson olefination • Vinyl boronate

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[20] All our reactions were carried out on 0.4 mmol scale but to assess the scalability of our methodology, we performed a scale-up reaction of 1a and benzaldehyde on a 1 mmol scale, yielding **2a** in 52 % yield.

[21] All calculations were performed at the LCCSD/6-311+G**(CH_2Cl_2)//B3LYP-D3/6-31+G*(CH_2Cl_2) level of theory using Jaguar 8.5 and ORCA 5.0.3. See SI for computational details.

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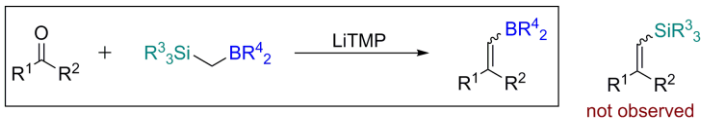

- Total chemoselectivity
- Mechanistic studies
- Understanding the influence of R^{1-4}
- 18 examples
- Low stereoselectivity

We have investigated the possibility of synthesizing substituted vinyl boronates from *gem*-borylsilylmethane derivatives using the Peterson olefination. Our results show a total chemoselectivity for the Peterson olefination over the boron-Wittig reaction, and a low *Z* selectivity, regardless of the nature of the carbonyl partner. A mechanistic study helps explain observed reactivity, chemoselectivity and stereoselectivity.