COMMUNICATION

A modular olefination reaction between aldehydes and diborylsilylmethide lithium salts.

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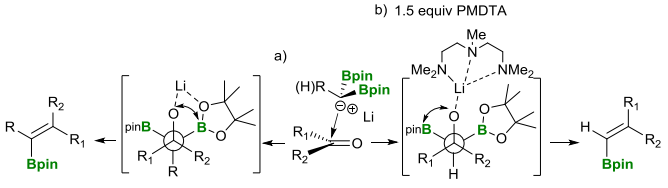
We describe the preparation of densely functionalised 1,1,-silylborylated trisubstituted alkenes, via boron-Wittig reaction, between LiC(Bpin)$_2$(SiMe$_3$) and aliphatic or aromatic aldehydes. The condensation of diborylsilylmethide lithium salts with α,β–unsaturated aldehydes provides a direct pathway to synthesize 1,1,-silylborylated conjugated dienes and diynes.

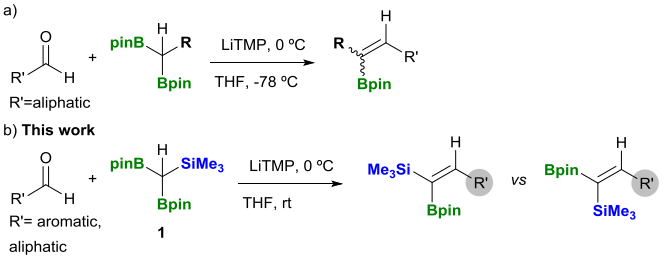
The condensation reaction between carbonyl substrates and α-boryl carbanions, appointed as boron-Wittig reaction, is considered of great synthetic utility for the preparation of valuable alkenes.[1] The renaissance of the boron-Wittig reaction in 2010, has firmly consolidated the benefits of this type of condensation reaction using stable pinacolboryl (Bpin) moieties in the α-boryl carbanions, but also controlling the stereoselectivity of the alkenes formed. Endo and Shibata explored the *in situ* deprotonation of 1,1-organodiboronates with LiTMP to obtain the stable lithium diborylcarbanions that underwent subsequent nucleophilic addition to a series of ketones suggesting that the stereoselectivity of the *syn*-B-O elimination might be controlled by the lithium interaction to one of the oxygens on the Bpin fragment (Scheme 1a).[2] Further independent work by Grygorenko[3a] and Morken[3b] have explored the boron-Wittig olefination of ketones with bis(pinacolboryl)methane in order to obtain trisubstituted alkenes with a significant control of the stereoselectivity, depending on the substrate and amine additives (Scheme 1b).



Scheme 1. Boron-Wittig reaction of ketones for tri- and tetrasubstituted alkenes.

The synthesis of trisubstituted vinyl boronates, via boron–Wittig reaction between geminal bis(boronates) and linear or α-branched aldehydes, was addressed by Morken and co-workers, with relative control on the selectivity (Scheme 2a).[4] As a trend, they observed that *E* isomer can be favoured when either large boronate substituents (R) or large aldehyde substituents (R') are employed. In contrast, when small aldehydes (i.e., linear alkyl) and small boronates are employed, the *Z* isomer seems to be favoured. However, aromatic aldehydes were not studied in that condensation reaction.

Attending to the challenging boron-Wittig reaction when aldehydes are involved, we became interested to launch a systematic study on the olefination with both aromatic and aliphatic aldehydes in the presence of the reagent HC(Bpin)$_2$(SiMe$_3$) (**1**) with the aim to get insights about the stereoselectivity on the formation of densely functionalised 1,1,-silylborylated trisubstituted alkenes (Scheme 2b). The introduction of silyl groups in the polyborylated reagent can be used as an alternative strategy to control the stereoselectivity on the boron Wittig reactions, as well as a direct methodology to introduce an extra functionality, however to the best of our knowledge only two approaches have been reported to date.[5,6]



Scheme 2. Boron-Wittig reaction of aldehydes with a) HC(Bpin)$_2$(R), b) HC(Bpin)$_2$(SiMe$_3$) for trisubstituted alkene synthesis.

The reagent HC(Bpin)$_2$(SiMe$_3$) (**1**) was deprotonated in the presence of LiTMP, to form a diborylsilyl stabilised carbanion at 0ºC. As a model substrate, benzaldehyde was added to the *in situ* prepared LiC(Bpin)$_2$(SiMe$_3$) in THF, at 0ºC. The reaction was warmed to room temperature and stirred for 16h to accomplish

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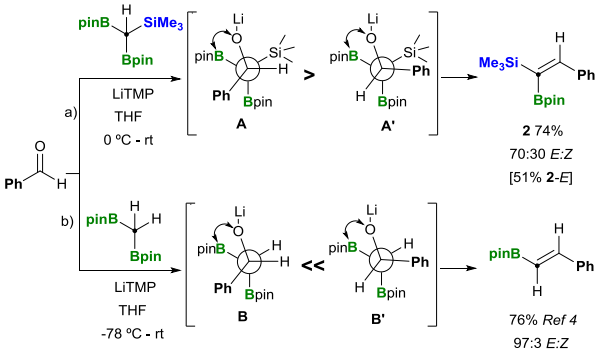
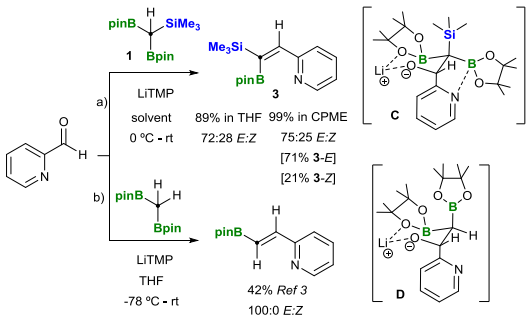
the formation of the 1,1-silylborylated trisubstituted alkene **2**, proving that B-O elimination is favoured versus Si-O Peterson elimination.[7] The selectivity observed shows a preference for the **2**-*E* stereoisomer with the Bpin moiety *syn* with respect to the aryl group, suggesting a favoured intermediate **A** versus **A'** (Scheme 3a). This is in contrast to the trend observed by Morken and co-workers, on the boron-Wittig olefination between bis(pinacolboryl)methane and aldehydes, in the presence of LiTMP, to furnish *trans*-vinylboronate esters, through a plausible favoured **B'** intermediate (Scheme 3b).[4] Despite the fact that the *E:Z* ratio for **2** is modest, it is noticeable to mention that the **2**-*E* isomer has never been isolated before. In fact, previous synthetic attempts, based on the hydroboration of 1-phenyl-2-trimethylsilylacetylene, provided only the **2**-*Z* isomer as an expected B-H *syn* addition to the triple bond.[8]

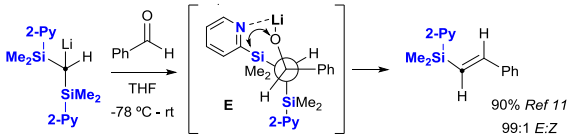


Scheme 3. Boron-Wittig reaction between benzaldehyde and a) $LiC(Bpin)_2(SiMe_3)$ and b) $LiCH(Bpin)_2$ for comparison.

We next explored the condensation of picolinaldehyde with **1**/LiTMP and the observed *E:Z* ratio on the trisubstituted alkene **3** increased slightly in THF or CPME as solvent (Scheme 4a), being the first synthetic approach towards the **3**-*E* since the **3**-*Z* was prepared from catalytic hydroboration strategies.[8c] The stereocontrol with $LiC(Bpin)_2(SiMe_3)$ contrasts with the one observed using $LiCH(Bpin)_2$, since the *trans*-vinylboronate ester is generated exclusively in 42% yield (Scheme 4b).[3] Considering the plausible chair-like intermediate, an intramolecular interaction between the N and the Bpin moiety, forming a five member ring in **C**, might explain the observed enriched selectivity on **3**-*E*.[9] In fact, product **3**-*Z* shows a characteristic ^{11}B NMR signal at 32.5 ppm, whereas for **3**-*E* the signal appears at 27.6 ppm as a consequence of the subtle N-B intramolecular interaction. Scheme 4b shows that in the absence of chelation control, the intermediate **D** might predict the *trans*-vinylboronate ester formation.[10] For comparison, Yoshida and co-workers found that the reagent $LiCH(SiMe_2(2\text{-}Py)_2)$ reacts with aldehydes to give the corresponding *trans*-vinylsilanes presumably via stereodetermining intermediate **E** where the intramolecular chelation of the pyridyl group with Li^+ locks the conformation (Scheme 5).[11] That is an interesting point since the alternative reaction between benzaldehyde and the reagent $LiCH(SiMe_3)_2$ produces the vinylsilanes only in *E:Z* ratio = 58:42.[12,13]

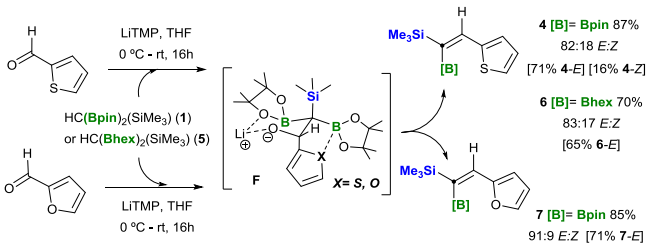


Scheme 4. Boron-Wittig reaction between picolinealdehyde and a) $LiC(Bpin)_2(SiMe_3)$ and b) $LiCH(Bpin)_2$ for comparison



Scheme 5. Boron-Wittig reaction between benzaldehyde and $LiCH(SiMe_2(2\text{-}Py)_2)$.

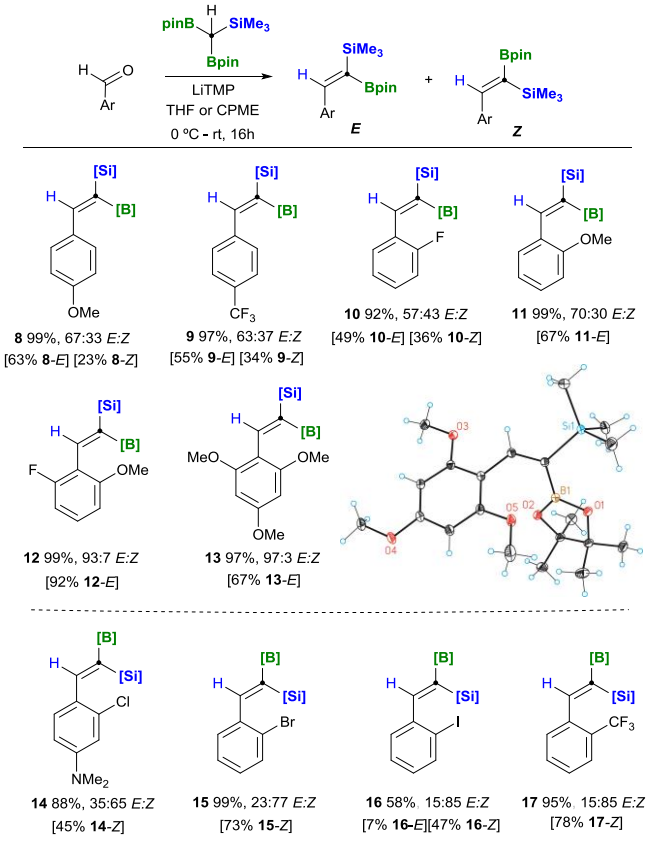
Next, we observed that the boron-Wittig reaction of thiophene-2-carbaldehyde and **1**/LiTMP produces the corresponding trisubstituted alkene **4** in an improved *E:Z* ratio = 82:12 (Scheme 6). Interestingly, **4**-*E* is synthetised for the first time in this work whereas **4**-*Z* had been prepared through acid Lewis $HB(C_6F_5)_2$-catalysed hydroboration of trimethyl(thiophen-2-ylethynyl)silane in 50% yield.[14] Alternatively, we studied the condensation of thiophene-2-carbaldehyde with $LiC(Bhex)_2(SiMe_3)$ (Bhex= hexylene glycolato boryl), generated *in situ* from $HC(Bhex)_2(SiMe_3)$ (**5**) and LiTMP. The product **6** was obtained with a *E:Z* ratio 83:17, although the conversion was reduced to 70% probably due to the steric hindrance associated to the Bhex moiety (Scheme 6). The ^{11}B NMR signal at 28.9 ppm for **6**-*E* might correlates with a subtle S-B intramolecular interaction. Furan-2-carbaldehyde reacted with **1**/LiTMP providing a similar reaction outcome towards the trisubstituted alkene **7** with a notably increased *E:Z* ratio 91:1, using both THF or CPME as solvent (Scheme 6). The intermediate **F** has been suggested to justify the enhanced stereoselectivity observed in this reaction, through a plausible intramolecular X--B interaction (X=O, S). Compound **7** has been prepared for the first time in this work.



Scheme 6. Boron-Wittig reaction between thiophene-2-carbaldehyde or furan-2-carbaldehyde with $LiC(Bpin)_2(SiMe_3)$ or $LiC(Bhex)_2(SiMe_3)$.

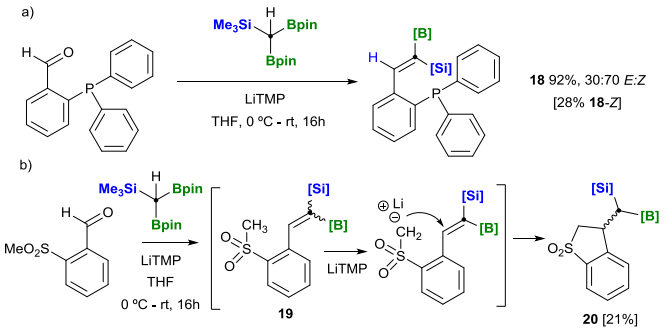
Next, we performed several experiments to demonstrate that steric and electronic modifications on aryl aldehyde substrates contributed not only to obtain the exclusive formation of stereoisomer *E*, but also to reverse the stereocontrol toward formation of stereoisomer *Z*, depending on the substituents present in the aryl group. Electron donating and electron withdrawing groups in *para* position do not change the reaction

outcome with a modest preference for the *E*-**8** and *E*-**9** stereoisomers (Scheme 7). Both are synthetised for the first time in this work, since only stereoisomers *Z*-**8** and *Z*-**9** are known.[8c,d,15] However, OMe substituents in *ortho* position seem to have a major influence on the *E*-stereocontrol for *E*-**11** and *E*-**12** in comparison to the influence of F towards *E*-**10** (Scheme 7). However, higher stereoselectivity is achieved when substrate 2,4,6-$(OMe)_3$-C_6H_2 is transformed into product **13** in 97% yield as *E:Z* ratio 97:3 (Scheme 7). X-Ray diffraction of *E*-**13** shows a short B_1-O_5 length distance (2.76 Å) compared to B_1-O_3 (4.81 Å), forcing a torsion angle C-C=C-C about 12.02º. It is suggested an attractive interaction between B_1-O_5 since the covalent bonds lengths are B_1-O_1 1.3796(8) and B_1-O_2 1.3794(8). None of these polyfunctionalised products with *ortho* substituents have been prepared before.Interestingly, when the *ortho* substituents are Cl, Br, I or CF_3, we noticed that the *Z* stereoisomers became preferred in products **14**-**17**.[16] The reversed trend might be correlated with steric effects of the silyl group that controls the B-O elimination towards the preferred products **16** and **17** as *E:Z* 15:85 ratio (Scheme 7).



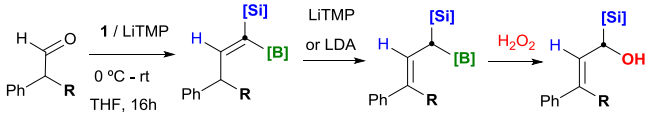
Scheme 7. Substrate scope for stereoselective boron-Wittig reaction with $HC(Bpin)_2(SiMe_3)$ (**1**) and LiTMP.

Similarly, sterically hindered *ortho* substituents are also compatible with the boron-Wittig reaction, as it has been seen in the synthesis of triaryl phosphine **18** in high yield and preference on the Z stereoisomer (Scheme 8a). Surprisingly, when 2-(methylsulfonyl)benzaldehyde reacted with reagent **1**/LiTMP, the expected trisubstituted alkene **19** was scarcely isolated (17% **19**-*E*), instead the cyclic system **20** was detected and isolated (Scheme 8b). Its formation might be postulated throughout the formation of (phenylsulfonyl)methylene lithium intermediate (via deprotonation of the aryl sulfonyl group with the excess of LiTMP)[17] which interacts intramolecularly with the alkene to form the cyclic saturated compound **20**. This type of benzothiophene 1,1-dioxides have been prepared through catalysed hydrogenation of the corresponding cyclic unsaturated substrates.[18]



Scheme 8. Boron-Wittig reaction between sterically hindered *ortho* substituted aryl aldehydes and $HC(Bpin)_2(SiMe_3)$ (**1**) / LiTMP.

The olefination of aliphatic aldehydes with **1**/LiTMP has demonstrated that steric factors might also influence the stereoselective reaction outcome. Whereas the boron-Wittig of 2-phenylacetaldehyde generates the corresponding trisubstituted olefin **21** in 75:25 *E:Z* ratio, the olefination of substrate 2-phenylpropanal increases the ratio up to 86:14 *E:Z* in **22**. Interestingly, the most sterically hindered substrate, 2,2-diphenylacetaldehyde, is transformed exclusively towards the *E*-**23** stereoisomer (Scheme 9). All these products could be converted into valuable allylic 1,1-borylsilylalkanes by proton abstraction/isomerization in the presence of LiTMP or LDA. The allylic compounds **24**-**26** could be isolated in moderate yield with exclusive *E* stereoselectivity and efficiently oxidised towards α-(hydroxyallyl)silanes **27**-**29** (Scheme 9).

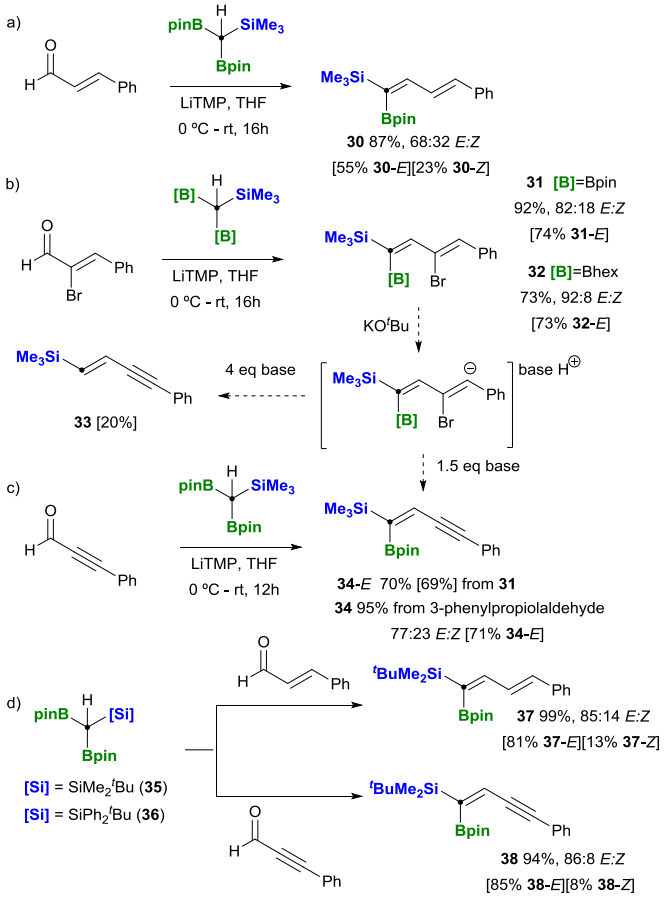


21 R= H 96%, 75:25 *E:Z* [63% **21**-*E*][21%**21**-*Z*]
22 R= Me 72%, 86:14 *E:Z* [60% **22**-*E*]
23 R= Ph 99%, 100:0 *E:Z* [98% **23**-*E*]
24 R= H [65%]
25 R= Me [15%]
26 R= Ph [33%]
27 R= H [92%]
28 R= Me [93%]
29 R= Ph [95%]

Scheme 9. Selective trend in olefination of aliphatic aldehydes with $HC(Bpin)_2(SiMe_3)$/LiTMP and subsequent proton abstraction/ isomerization and eventual oxidation.

Finally, we explored the olefination of α,β-unsaturated aldehydes with $HC(Bpin)_2(SiMe_3)$ / LiTMP, resulting in a chemoselective preference on the nucleophilic attack of diborylsilylmethide lithium salt to the aldehyde functionality versus the conjugated β position. Scheme 10 shows that cinnamaldehyde condense with $LiC(Bpin)_2(SiMe_3)$ to give the trisubstituted conjugated dienyl compound **30** in 68:32 *E:Z* ratio, however the analogue substrate 2-bromo-3-

phenylacrylaldehyde conducted the boron-Wittig reaction with LiC(Bpin)$_2$(SiMe$_3$) towards the preferred formation of **31** in 82:18 *E:Z* ratio. Even higher stereoselectivity could be achieved using reagent LiC(Bhex)$_2$(SiMe$_3$), generating product *E*-**32** in 92:8 *E:Z* ratio (Scheme 10). Interestingly, the addition of 1.5 equiv of KO^{t}Bu to **31** contributed to the HBr elimination and subsequent diyne *E*-**34** formation with exclusive stereoselectivity (Scheme 10). However, the addition of an excess of base resulted in a complete proto-deborylation process with the concomitant formation of (*E*)-trimethyl(4-phenylbut-1-en-3-yn-1-yl)silane (**33**). To have a complete picture of the olefination of α,β-unsaturated aldehydes, we conducted the boron-Wittig condensation between 3-phenylpropiolaldehyde and reagent **1**. As Scheme 10 shows, chemoselective formation of product **34** could be attained although with lower stereoselectivity, in comparison to *E*-**34** formed from **31**. We have investigated the substituent effect of the silane group on E/Z selectivities. The reagents LiC(Bin)$_2$[Si] (**35,** ([Si]=SiMe$_2$^{t}Bu)) **36,** ([Si]=SiPh$_2$^{t}Bu) have been synthesized[19] and the stereoselectivity on the boron-Witing indicates that the stereoselectivity on the E stereoisomer is favoured when the more sterically hindered substituents in **35** are involved (Scheme 10, products **37** and **38**), although with reagent **36** the conversion was very low, probably due to the highly congested diborylmethylsilane.



Scheme 10. Chemo and streoselective boron-Wittig reaction with α,β-unsaturated aldehydes.

In summary, we have conducted the olefination reaction between aromatic or aliphatic aldehydes and LiC[B]$_2$[Si] ([B]= Bpin or Bhex, [Si]= SiMe$_3$, SiMe$_2$^{t}Bu, SiPh$_2$^{t}Bu) with an special focus on the challenging stereocontrol on the 1,1-silylborylated trisubstituted alkene formation. We have found that picolinaldehyde, thiophene-2-carbaldehyde and furan-2-carbaldehyde could be involved in stereodetermining intermediates via intramolecular interaction of N, S or O with B. Also a divergent stereocontrol has been observed when OMe *ortho* substituents in the aromatic aldehydes favour the *E*-borylsilylalkane formation whereas halide *ortho* substituents stabilises the Z-borylsilylalkanes. The condensation of α,β–unsaturated substrates with LiC(Bpin)$_2$[Si] allows access to 1,1-silylborylated conjugated dienes and diynes, with relative high stereoselectvity.

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