Alkenylboronic ester activation to nucleophilic addition and electrophilic trapping with carbonyl groups

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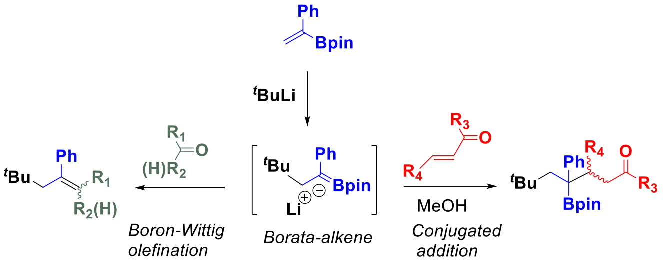
Dedicated to Prof. Masahiro Murakami
for his inspiring research career



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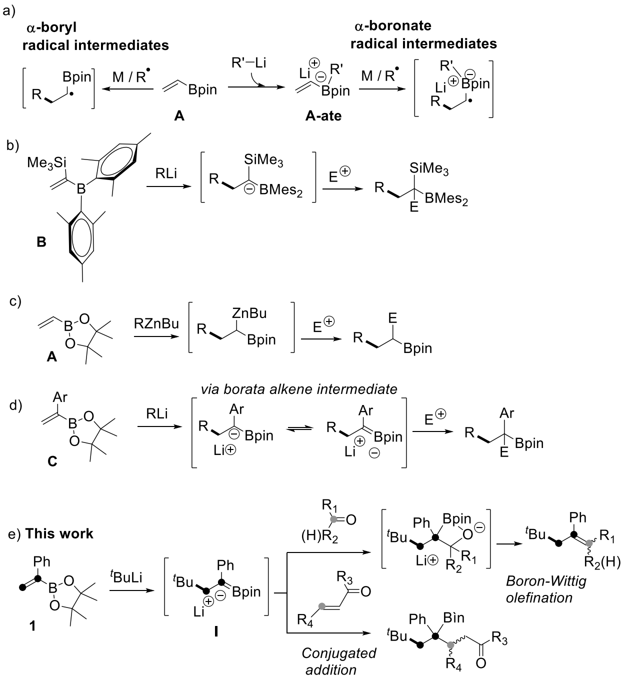
Abstract: Carbolithiation of 1-phenylvinylboronic acid pinacol ester with tert-butyl lithium was used to generate α-phenylboryl carbanions which were reacted in a straightforward manner with carbonyl groups via boron-Wittig sequence. When unhindered α,β-unsaturated carbonyl compounds were used, 1,4-addition of the α-phenylboryl carbanions was observed over the boron-Wittig sequence.

Key words alkenylboronates, borata-alkene, Boron-Wittig, boron-ate suppression, α-boryl carbanions

Functionalization of C(sp^2)-B in alkenylboronic esters is considered an efficient strategy towards stereoselective synthesis of substituted alkenes and dienes.[1,2] But the vinylborane functional group represents an additional synthetic opportunity to react through the alkene π-system due to the adjacent empty p orbital on boron atom. The formation of stable α-boryl radical[3-9] and α-boron"ate" radical[10-13] intermediates has been postulated to be involved in 1,2-difunctionalization of alkenylboronic esters (Scheme 1). However, the alternative nucleophilic addition to the alkene π-system in vinylboranes has been scarcely succeeded due to the competitive boron"ate" (**A-ate**) formation. Suppression of the "ate" complex formation can be sterically prevented by using substituted hindered arylboranes, such as dimesitylboranes.[14-16] Cooke and co-workers have demonstrated the feasible nucleophilic addition of organolithium reagents to α-substituted vinyldimesitylborane **B**, followed by electrophilic trapping with MeI (Scheme 1b).[17] Nakamura and co-workers extended this concept towards the organozinc nucleophilic addition to vinylpinacolborane **A**, with subsequent electrophilic trapping via *gem*-zincio/boryl intermediates (Scheme 1c).[18] In this context, our group has recently demonstrated the polar addition of alkyllithium reagents to the terminal carbon of 1-arylvinylboronic acid pinacol ester **C**, in basis to the enhanced stability of the resulting α-arylboryl carbanion, followed by electrophilic trapping with a series of C(sp^3)X, via substitution pathways (Scheme 1d).[19] With this 1,2-dicarbofunctionalization protocol we have been able to generate two new C(sp^3)–C(sp^3) bonds across the alkene, delivering valuable tetrasubstituted carbon centers, in the absence of catalyst, additives or any type of radical initiators. We based our new reactivity on the remarkable stability of the α-arylboryl carbanion due to the valence deficiency of the adjacent three coordinate boron center, postulating the corresponding borata-alkene resonance form (Scheme 1d).[20,21]

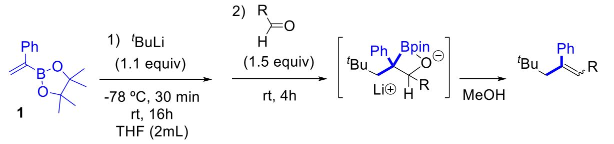
Next we hypothesized about the nucleophilic addition to vinylborane **C** followed by electrophilic trapping with carbonyl functional groups, aldehydes and ketones. Murakami and co-workers were pioneers to study the allylation reaction of aldehydes with 1-alkenylboronates, which acted as the synthetic equivalent to γ-substituted allylboronates, in the presence of cationic rhodium(I) catalysts.[22] Here, we report the feasibility to perform the alkyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by the trapping of α-arylboryl carbanion **I** with carbonyl groups, that eventually proceeds through a B-O elimination to generate tri or tetrasubstituted alkenes, as a Boron Wittig sequence (Scheme 1e).[23] But also, we have demonstrated that the electrophilic trapping can chemoselectively be performed through 1,4-addition on α,β-unsaturated carbonyl compounds (Scheme 1e).

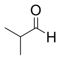
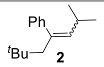
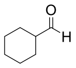
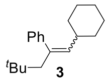
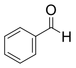
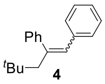
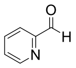
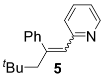
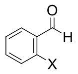
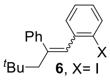
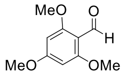
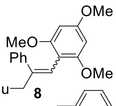
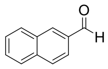
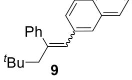
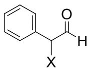
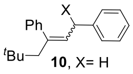


Scheme 1. Activation of alkenylboronic esters as electron acceptor motifs through the alkene π-system

From the outset, we prepared the borata-alkene intermediate **I** by addition of 1.1 equiv of ^{t}BuLi to 1-phenylvinylboronic acid pinacol ester **1**, at -78 °C for 30 minutes, during 16 h at room temperature, in THF as solvent. Subsequently, 1.5 equiv of isobutyraldehyde were added and the reaction mixture was stirred for 4 h. Substrate **1** was converted into product **2** in 74% by NMR (in comparison with internal standard naphthalene) and 70% isolated yield (Table 1, entry 1). We observed the formation of both diastereoisomers which were purified together. Similar reaction outcome has been experimented when cyclohexanecarbaldehyde was the electrophilic partner involved (Table 1, entry 2). Alternatively, benzaldehyde reacted with lower conversion and similar diastereoselection, although pinacolinaldehyde showed a remarkably enhanced reactivity, suggesting a marked influence of electronic issue during the electrophilic trapping (Table 1, entries 3,4). However, although we speculated about a plausible interaction of N with Bpin moiety to favour the formation of one specific diastereoisomer, based on the Boron-Wittig reaction between picolinealdehyde and LiC(Bpin)$_2$(SiMe$_3$),[24] in our case no stereopreference was observed. Both diastereoisomers could be isolated separately and identified by 1D-NMR NOE experiments.

Table 1. Tert-butyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by trapping with aldehydes[a]



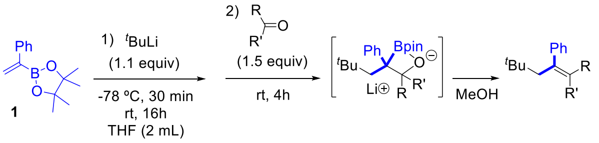
Entry	Aldehyde	Product	Conversion (%)	Isolated Yield [%]	d.r. (*E/Z*)
1		 **2**	74	70	1/1[b]
2		 **3**	73	69	1/1[b]
3		 **4**	35	33	1/1[b]
4		 **5**	90	84	1/1[c]
5 6		 **6**, X= I **7**, X= CF$_3$	X= I, 59 X= CF$_3$, 74	56 69	1/1[b] 4/5[b,c]
7		 **8**	96	92	1/3[b,c]
8		 **9**	49	48	1/1[b]
9 10		 **10**, X= H **11**, X= Ph	X= H, 42 X=Ph, 65	38 58	1/1[c] 1/1[c]

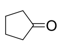
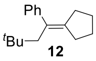
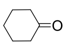
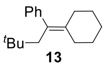
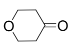
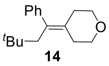
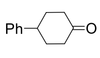
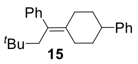
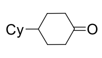
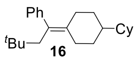
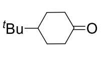
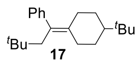
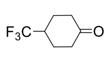
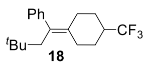
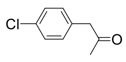
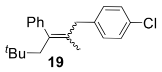
[a]Reaction conditions: 1) **1** (0.3 mmol), ^{t}BuLi (0.33 mmol), THF (2 mL), -78 °C, 30 min, and then rt, 16h; 2) aldehyde (0.45 mmol), rt, 4h, and MeOH (2mL). Conversion and d.r. calculated by ^{1}H NMR spectroscopy with naphthalene as internal standard. [b]Isolated as mixture of diastereosiomers. [c]Isolated as pure *E* and *Z* diastereoisomers.

Next, we introduced steric hindrance on the *ortho* position of the benzaldehyde, X=I and CF$_3$, but the diastereoselectivity in the alkene products was (*E*:*Z*) = 1/1 and 4/5, respectively (Table 1, entries 5,6). Interestingly, when the sterically hindered aldehyde 2,4,6-(OMe)$_3$-C$_6$H$_2$CHO was involved in the electrophilic trapping, the conversion was the highest achieved on the trisubstituted alkene and the diastereoselection was 1:3 (*E*:*Z*), as we unambiguously proved by 1D-NMR NOE experiments on the isolated major diastereoisomer *Z* (Table 1, entry 7). Ultimately, 2-naphthaldehyde, 2-phenylacetaldehyde and 2,2-diphenylacetaldehyde were converted through this 1,2-dicarbofunctionalization reaction, although moderate yields were achieved with 1/1 dr (Table 1, entries 8-10). For products **10** and **11**, both diastereoisomers could be isolated separately and characterized accordingly to 1D-NMR NOE experiments.

The scope of cyclic ketones was next examined to prove the electrophilic trapping after ^{t}BuLi activation of **1** (Table 2). Cyclopentanone, cyclohexanone and tetrahydro-4H-pyran-4-one reacted with the borata-alkene intermediate **I** to give the corresponding tetrasubstituted alkenes **12**-**14**, (Table 2, entries 1-3), being the transformation of cyclohexanone the most efficient (81% isolated yield, Table 2, entry 2).

Table 2. Tert-butyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by trapping with ketones[a]



Entry	Ketone	Product	Conversion (%)	Isolated Yield [%]	d.r.
1		 **12**	72	68	---
2		 **13**	87	81	---
3		 **14**	66	59	---
4		 **15**	85	77	---
5		 **16**	77	70	---
6		 **17**	85	83	---
7		 **18**	78%	73%	---
8		 **19**	54%	52%	1/1[b]

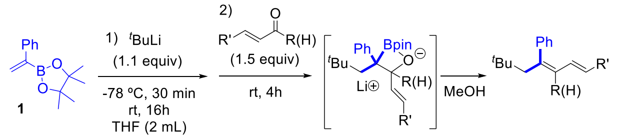
[a]Reaction conditions: 1) **1** (0.3 mmol), ^{t}BuLi (0.33 mmol), THF (2 mL), -78 °C, 30 min, and then rt, 16h; 2) ketone (0.45 mmol), rt, 4h, and MeOH (2mL). Conversion and d.r. calculated by ^{1}H NMR

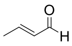
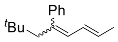
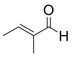
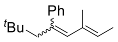
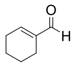
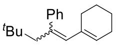
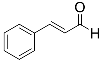
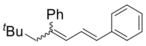
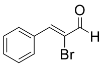
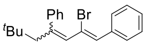
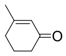
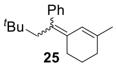
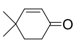
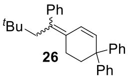
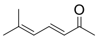
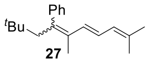
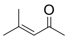
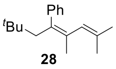
spectroscopy with naphthalene as internal standard. [b]Isolated as mixture of diastereosiomers.

An electronically and sterically diverse array of 4-substituted cyclohexanone were next studied (Table 2, entries 4-7) and 4-(tert-butyl)cyclohexan-1-one provided the corresponding alkene **17** with the highest isolated yield (83%, Table 2, entry 6). When the acyclic ketone 1-(4-chlorophenyl)propan-2-one was explored for the electrophilic trapping, the tetrasubstituted alkene **19** could be isolated in 52% yield, with dr = 1/1 (Table 2, entry 8).

Subsequent study involved α,β-unsaturated aldehydes and ketones, with the aim to explore the chemoselectivity of the electrophilic trapping sequence. When (*E*)-but-2-enal, (*E*)-2-methylbut-2-enal and (*E*)-2-methylbut-2-enal were added to react with the borata-alkene intermediate **I**, the trapping of the aldehyde functionality took place chemoselectively, to give the corresponding conjugated dienes **20**-**22**, although in low yield and dr = 1:1 (Table 3, entries 1-3).

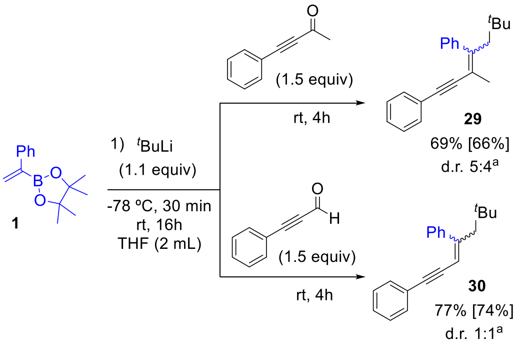
Table 3. Tert-butyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by trapping with α,β-unsaturated aldehydes and ketones[a]



Entry	Aldehyde	Product	Conversion (%)	Isolated Yield [%]	d.r.
1		 **20**	19	17	1/1[b]
2		 **21**	49	47	1/1[b]
3		 **22**	39	31	1/1[b]
4		 **23**	61	58	1/1[b]
5		 **24**	45	43	1/1[b]
6		 **25**	67	62	1/1[b]
7		 **26**	77	76	1/1[b]
8		 **27**	55	48	1/1[b]
9		 **28**	24	21	1/0[c]

[a]Reaction conditions: 1) **1** (0.3 mmol), ᵗBuLi (0.33 mmol), THF (2 mL), -78 °C, 30 min, and then rt, 16h; 2) α,β-unsaturated aldehydes and ketones (0.45 mmol), rt, 4h, and MeOH (2mL). Conversion and d.r. calculated by ^{1}H NMR spectroscopy with naphthalene as internal standard. [b]Isolated as mixture of diastereosiomers. [c]Isolated as pure diastereoisomers.

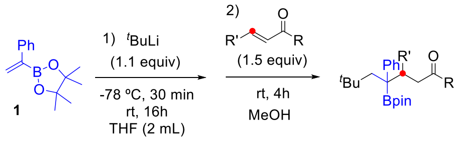
With the aim to facilitate the conjugate addition through the electrophilic trapping sequence, we hypothesized about the use of cinnamaldehyde and (*Z*)-2-bromo-3-phenylacrylaldehyde. However, in both cases the Boron Wittig reaction took place chemoselectivity, in moderate yield towards dienes **23** and **24** (Table 3, entries 4,5). Next, we studied the effect of the 1,2-dicarbofunctionalization with cyclic and acyclic α,β-unsaturated ketones, and we found that formation of dienes and trienes **25**-**27** were achieved chemoselectively in moderate yield (Table 3, entries 6-8), and the polysubstituted diene **28** with total diastereoselectivity, probably due to the enhanced steric hindrance around the enolate intermediate (Table 3, entry 9). Remarkably, the formation of substituted enynes **29** and **30**, was achieved through the 1,2-dicarbofunctionalization of **1** involving 4-phenylbut-3-yn-2-one and 3-phenylpropiolaldehyde, although with dr= 5/4 and 1:1, respectively (Scheme 2). The reaction proceed chemoselectively though Boron-Wittig sequence, althoughmoderate yields.

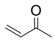
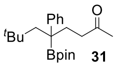
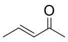
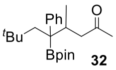
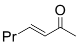
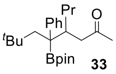
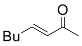
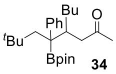
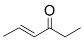
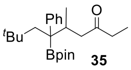
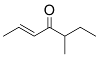
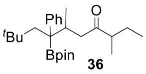
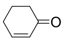
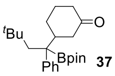
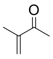
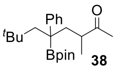


Scheme 2. Tert-butyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by trapping with 4-phenylbut-3-yn-2-one and 3-phenylpropiolaldehyde. [a]Isolated as pure diastereoisomers.

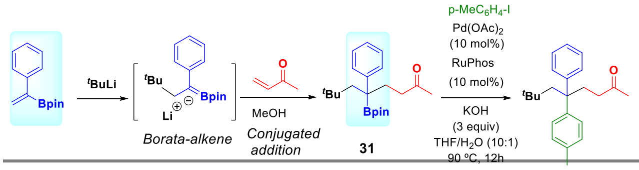
Surprisingly, when the α,β-unsaturated ketone but-3-en-2-one was studied for the electrophilic trapping of the borata-alkene intermediate **I**, we observed the exclusive formation of 7,7-dimethyl-5-phenyl-5-(pinacolboryl)octan-2-one (**31**) as a result of the 1,4-addition (Table 4, entry 1). This remarkable observation gave us the opportunity to explore a related substrate scope of unhindered α,β-unsaturated ketones. In that context, (*E*)-pent-3-en-2-one, (*E*)-hept-3-en-2-one and (*E*)-oct-3-en-2-one reacted with the borata-alkene intermediate **I** via chemoselective conjugated addition giving access to products **32**-**34**, in moderate yields, (Table 4, entries 2-4). Similarly, larger substituents on the ketone substrate were compatible with the 1,4-addition sequence, achieving isolated yields up to 73% or 72% for product **35** and **36** (Table 4, entries 5,6). The diastereoselectivity was not full controlled, being slightly increased when bulky substituents in C_β were involved (see dr= 10/7 in product **34**, Table 4, entry 4). Tert-butyllithium activation of **1** followed by trapping with cyclohex-2-en-1-one allowed the efficient conjugated addition towards product **37**, although with dr= 1:1 (Table 4, entry 7). Product **38** was isolated as a single diastereoisomer although in low yield (Table 4, entry 8). In all the examples described, a new tetrasubstituted carbon center has been formed from 1-phenylvinylboronic acid pinacol ester substrate. It is noteworthy to mention that α-boryl carbanion-based conjugate additions remains scarcely explored, and the unique methods reported so far involve deborylation of geminal triboryl[25] and diborylalkanes[26,27] or alternative activation of diboryl allylic systems.[28] α-Boryl C(sp^2) nucleophiles can also be added to enones through 1,4-addition in the presence of Rh catalysts.[29] The feasibility of conjugate addition of α-boryl carbanion represents an emerging area and our approach becomes potentially useful since the α-arylboryl carbanion intermediate **I** is formed *in situ* from 1-phenylvinylboronic acid pinacol ester and tert butyllithium, which eventually reacts with the α,β-unsaturated ketones to generate the tetrasubstituted carbon center. The quaternary center can be easily achieved by cross coupling reaction of the tetrasubstituted carbon center as we illustrated in the transformation of **31** into product **39** via Suzuki-Miyaura cross coupling with p-MeC$_6$H$_4$I (Scheme 3).

Table 4. Tert butyllithium activation of 1-phenylvinylboronic acid pinacol ester (**1**), followed by conjugated addition to α,β-unsaturated ketones[a]



Entry	Aldehyde	Product	Conversion (%)	Isolated Yield [%]	d.r.
1		 **31**	43	39	---
2		 **32**	41	35	4/3^{b}
3		 **33**	54	50	3/2^{b,c}
4		 **34**	63	59	10/7^{b}
5		 **35**	79	73	5/3^{b}
6		 **36**	75	72	nd
7		 **37**	70	65	1/1^{b,c}
8		 **38**	53	27	---

[a]Reaction conditions: 1) **1** (0.3 mmol), ^{t}BuLi (0.33 mmol), THF (2 mL), -78 °C, 30 min, and then rt, 16h; 2) α,β-unsaturated ketones (0.45 mmol), rt, 4h, and MeOH (2mL). Conversion and d.r. calculated by ^{1}H NMR spectroscopy with naphthalene as internal standard. [b]Isolated as mixture of diastereosiomers. [c]Major diastereoisomer isolated.



39 [52%]

Scheme 3. Functionalization of **31** towards the generation of a quaternary centre through Suzuki-Miyaura cross coupling.

In conclusion, we have described that 1-phenylvinylboronic acid pinacol ester can be activated by nucleophilic attack of ^{t}BuLi, by suppression of any boron"ate" byproduct formation. The corresponing α-arylboryl carbanion is stabilized as a borata-alkene accumulating the nucleophilic character to react with aldehydes and ketones. The resulting α-arylboryl enolate intermediates evolve through B-O elimination to generate tri or tetrasubstituted alkenes and dienes, via Boron Wittig sequence, with little control on the diastereoselectivity. When unhindered α,β-unsaturated carbonyl compounds are involved, the electrophilic trapping is chemoselectively performed through 1,4-addition generating new tetrasubstituted carbon centers.

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Supporting Information

yes

Primary Data

no

Conflict of Interest

The authors declare no conflict of interest.

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