Diborylalkyl lithium salts trigger regioselective ring opening of vinyl aziridines.

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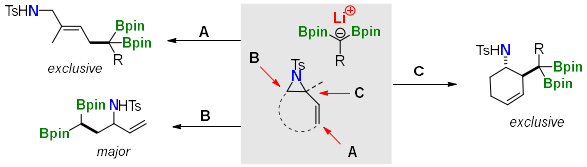
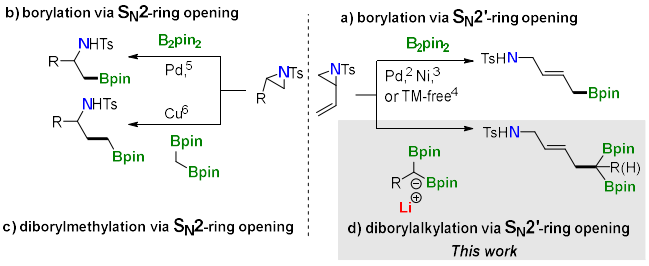


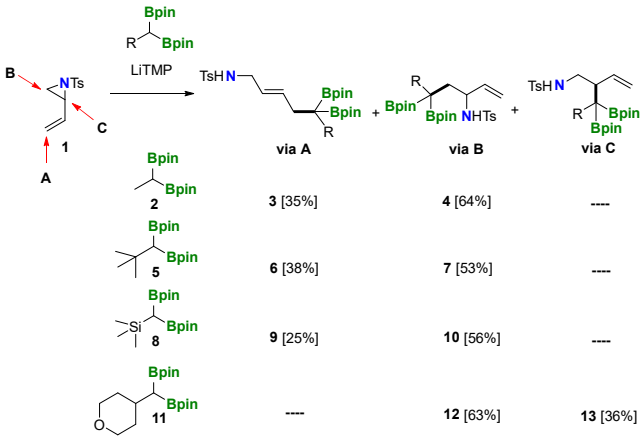
ABSTRACT: *gem*-Diborylalkanes treated with LiTMP produce α-diborylalkane lithium bases that perform nucleophilic attack on vinyl aziridines with controlled regioselectivity. Preferred S_N2 diborylalkylation ring opening reaction on the less sterically hindered position is observed with 1-tosyl-2-vinylaziridine whereas exclusive S_N2' nucleophilic attack occurs on 2-methyl-1-tosyl-2-vinylaziridine. Cyclic vinyl aziridines interact through a third venue, via S_N2 diborylalkylation ring opening reaction on the allylic position. Homoallylic diboronates are formed with complete stereochemical control.

Nucleophilic ring opening reactions involving the construction of useful organoboron molecular structures, combine the selective control of the ring cleavage together with total atom economy parameters.[1] Versatile allylic amines are efficiently formed from Pd,[2] Ni[3] or transition metal-free[4] catalyzed borylative S_N2' ring opening of vinyl aziridines with bis(pinacolato)diboron (B_2pin_2), along the concomitant formation of the allylic boronate functionality (Scheme 1a). Alternatively, S_N2 borylative ring opening reaction of aryl aziridines through a palladium catalyzed protocol, allows the formation of difunctional β-aminoboronate compounds (Scheme 1b).[5] The use of *gem*-diborylmethane instead of B_2pin_2 resulted in the formation of γ-aminoboronic esters through copper catalyzed ring opening / C-C bond formation of alkyl aziridines in the presence of LiO^{t}Bu (Scheme 1c).[6] However, to the best of our knowledge, the activation of *gem*-diborylalkanes with lithium bases to promote diborylalkylation ring opening of vinyl aziridines is unknown (Scheme 1d), despite the fact that the analogue reaction with epoxides[7] and vinyl epoxides[8] has recently been explored. The activation of *gem*-diborylalkanes with LiTMP via deprotonation and carbanion stabilization, allows that both boryl moieties remain in the final product.[9]



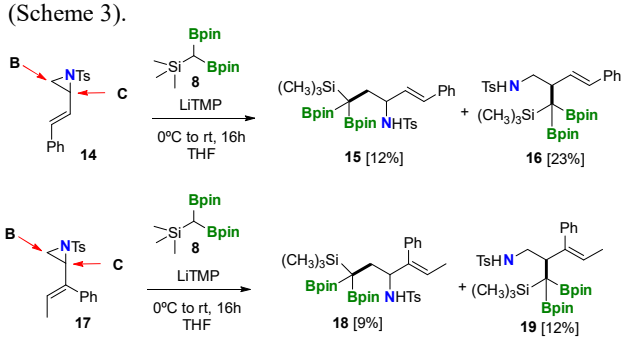
Scheme 1. C-B and C-C bond formation through ring opening of alkyl- aryl- and vinyl aziridines.

To study the viability of our work hypothesis we selected 1-tosyl-2-vinylaziridine (**1**) as model substrate, to react with $HC(CH_3)(Bpin)_2$ (**2**) in the presence of 1.2 equiv of LiTMP. When the reaction took place initially at 0ºC (10 min), followed by 16h at rt, the substrate was quantitatively transformed into two products. The major product was **4** (isolated yield 64%) formed via S_N2 diborylalkylation ring opening reaction on the less sterically hindered position (Scheme 2). However, the S_N2' ring opening reaction became competitive forming the *E*-homoallylboronate product **3** (Scheme 2). Similar reaction outcome was observed using the *gem*-diborylalkanes HC(^{t}Bu)$(Bpin)_2$ (**5**) and $HC(Si(CH_3)_3)(Bpin)_2$ (**8**) being the S_N2 ring opening / C-C coupling throughout the less sterically hindered position, the most favored reactivity (Scheme 2).



Scheme 2. Diborylalkylation ring opening reaction of 1-tosyl-2-vinylaziridine (**1**).

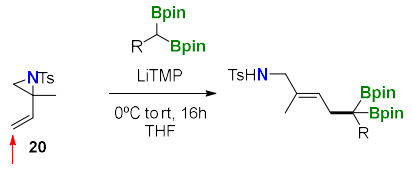
Interestingly, when (tetrahydro-2H-pyran-4-yl)methylenebispinacolboronate (**11**) was employed as the *gem*-diborylalkane reagent, the S_N2' ring opening reaction was weakened and only products formed via S_N2 pathway were isolated (63% due to the nucleophilic attack on the less sterically hindered position and 36% on the most congested position, (Scheme 2). Similar trend was detected when (E)-2-styryl-1-tosylaziridine (**14**) was treated with $HC(Si(CH_3)_3)(Bpin)_2$ (**8**) since S_N2' ring opening reaction was suppressed in favour of the nucleophilic attack on the more congested position, (Scheme 3). The analogue vinyl aziridine (E)-2-(1-phenylprop-1-en-1-yl)-1-tosylaziridine (**17**) also performed a favored diborylalkylation ring opening reaction through S_N2 ring opening, despite the fact that isolated yields on the products diminished significantly, probably due to the instability of the electronically conjugated allylic products (Scheme 3).



Scheme 3. Diborylalkylation ring opening reaction of substituted vinyl aziridines **14** and **17**.

To our delight, when 2-methyl-1-tosyl-2-vinylaziridine (**20**) was explored for diborylalkylation ring opening reaction with reagent $HC(Si(CH_3)_3)(Bpin)_2$ (**8**) and LiTMP, we observed the exclusive formation of the allylic amine / homoallylic boronate **21** as a result of the regioselective nucleophilic attack via S_N2' mechanism (Table 1, entry 1). To the best of our knowledge, this is the first example of a lithium stabilized α–diboryl carbanion reacting along conjugate addition, since it has only been reported that diborylmethide lithium salts transmetallate with zinc(II) halide to form the corresponding diborylmethyl zinc(II) species that interact with π-allyliridium intermediates to promote a S_N2 allylic substitution.[10] On the contrary, S_N2' allylic substitution of primary and secondary allylic chlorides with diborylmethane has been reported to proceed in the presence of Cu/NHC catalyst and LiO^{t}Bu (3 equiv), where the NHC ligand (IMes=1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene]) played an important role in the conjugated mechanism.[11] Even with sub-stoichiometric amounts of base (Cs_2CO_3, 0.5 equiv) in combination with MeOH as solvent and Cu(I) as catalyst without any ligand, it has been reported the deborylative allyl-alkyl coupling between diborylmethane and vinyl cyclic carbonates, throughout copper-catalyzed S_N2' ring opening pathway with extrusion of CO_2.[12] Diborylmethane can be also activated with Ag(I) to further transmetallation to π-allylpalladium intemediates in order to coduct the corresponding allyl-alkyl coupling, with the aid of an oxidant to regenerate the Pd (II) species.[13] All these Cu- and Pd- methods have in common that homoallylboronates are selectively formed through allylic reactions while deborylation is undertaken and consequently the final product contains only one boryl unit. Here we report and exclusive S_N2' ring opening of vinylaziridines through diborylalkyl lithium salts keeping the two boryl moieties unaltered in the final product. The reaction occurs with complete stereocontrol towards the formation of the (*E*)-isomer as it can be seen in Table 1. This fact was proved doing a NOE experiment of product **21** (See Supporting Information).

Tabe 1. Regioselective S_N2' diborylalkylation/ring opening of 2-methyl-1-tosyl-2-vinylaziridine (**20**)[a]



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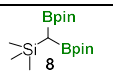
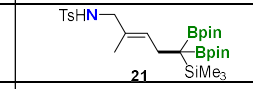
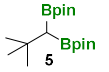
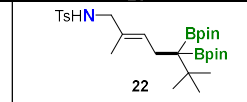
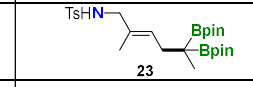
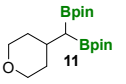
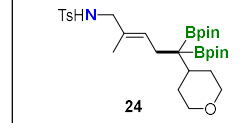
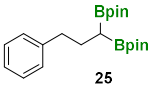
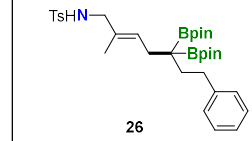
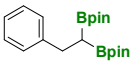
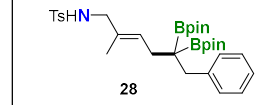
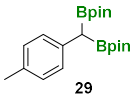
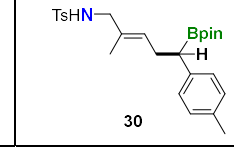
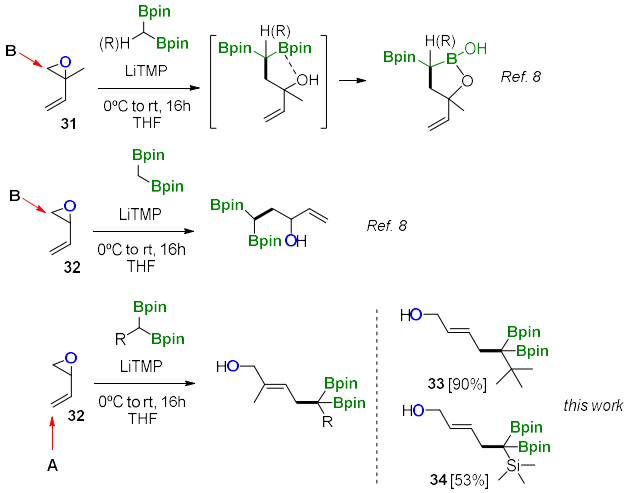
1			[93%]
2			[96%]
3			[98%]
4			[99%]
5			[50%]
6			[75%]
7			[65%]

[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), *gem*-diborylalkanes (0.5 mmol, 1 equiv), LiTMP (0.6 mmol, 1.2 equiv), THF (3 mL), rt, 16h.

When the *gem*-diborylalkanes involved in the reaction were **2**, **5** or **11**, containing primary, secondary and tertiary C_β substituents, the isolated yields on the desired product were quantitative (Table 1, entries 2-4). However, the *gem*-diborylalkanes **25** and **27**, containing 1-phenyl-ethyl and benzyl substituents, respectively, proceed towards the ring opening C-C cross coupling in moderate isolated yield (Table 1, entries 5-6). Interestingly, the reaction with $HC(p\text{-}MeC_6H_4)(Bpin)_2$ (**29**) allowed the reaction to take place efficiently, although protodeboronation occurred towards the formation of product **30** containing only one boryl moiety (Table 1, entry 7). We suggest that steric hindrance

around the α–diboryl carbanion might justify the favoured protodeboronation under basic conditions.[14]

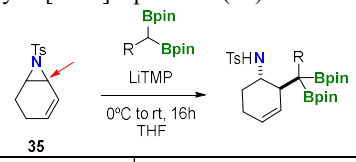
Remarkably, the observed regioselective diborylmethylation of vinyl aziridine **1** and **20** is significantly different to the one observed in the analogue vinyl epoxides **31** and **32**, under the same reaction conditions (Scheme 4). Nucleophilic attack of diboryllkyl lithium salts occurred exclusively at the homoallylic position of **31**, with concomitant intramolecular cyclization to give the substituted 3-borylated 1,2-oxaborolan-2-ol product (Scheme 4).[8] The substrate 2-vinyloxirane (**32**) also provides the S_N2 ring opening with $H_2CB_2pin_2$,[8] whereas the use of substituted diboryllkyl lithium salts favors the exclusive S_N2' ring opening / C-C coupling as we demonstrated in this work (Scheme 4).



Scheme 4. Diborylalkylation ring opening reaction of substituted vinyl epoxides **31** and **32**.

Next, we explored the diborylalkylation/ring opening of cyclic vinyl aziridines such as 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**35**)[15] and, in contrast to the observed S_N2' ring opening of non-cyclic vinylaziridine **20**, we found that **35** suffered a S_N2 nucleophilic attack at the allylic position, instead (Table 2). The reaction is stereocontrolled forming exclusively homoallyldiboronate species with *trans* disposition of the NHTs and $CR(Bpin)_2$ groups, keeping the two boryl moieties unaltered in the final product. With substituted *gem*-diborylalkanes **2**, **5**, **8** and **11**, containing primary, secondary and tertiary C_β substituents, the regioselective S_N2 ring opening was efficiently performed isolating quantitative percentages of the desired homoallyldiboronate products **36-39** (Table 2, entries 1-4). Reagent **27** containing the benzyl group, also allowed the formation of the desired homoallyldiboronate species **40** in moderate isolated yield (Table 2, entry 5). However, when the phenyl substituted *gem*-diborylalkane **29** is involved in the reaction, we observed that the coupled product **41** retained only one boryl moiety, suggesting the protodeboronation pathway as a consequence of the steric hindrance at the quaternary center (Table 2, entry 6).

Tabe 2. Regioselective $S_N2$diborylalkylation/ring opening of 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**35**)[a]



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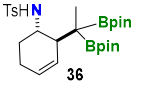
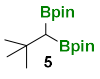
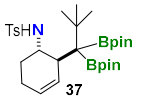
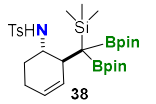
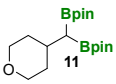
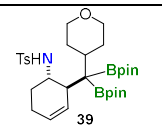
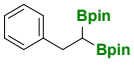
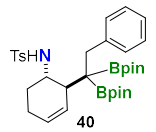
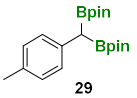
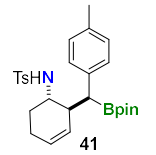
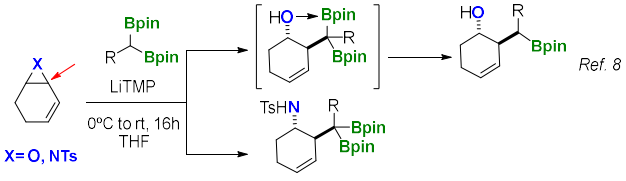
1	 2	 36	[98%]
2	 5	 37	[98%]
3	 8	 38	[99%]
4	 11	 39	[96%]
5	 27	 40	[51%]
6	 29	 41	[66%]

[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), *gem*-diborylalkanes (0.5 mmol), 1 equiv, LiTMP (0.6 mmol, 1.2 equiv), THF (3 mL), rt, 16h.

A similar protodeboronation sequence was involved in the diborylalkylation the analogue cyclic vinyl epoxide 3,4-epoxy-1-cyclohexene (**42**), providing the homoallylboronate products with only one boryl moiety at the final product, independently of R=aryl or alkyl group (Scheme 5).[6] It suggests that the OH functionality might favor the intramolecular deborylation in a sterically hindered quaternary C center,[16] whereas in the case of amine group this interaction might not be favored.



Scheme 5. Comparative diborylalkylation ring opening reaction of cyclic vinyl epoxide and vinyl aziridine.

It can be concluded that α-diboryl carbanions formed from *gem*-diborylalkanes and LiTMP, perform regioselective nucleophilic attack on vinyl aziridines. Preferred S_N2 ring opening / C-C bond forming on the less sterically hindered 1-tosyl-2-vinylaziridine in contrast to the favoured S_N2' diborylalkylation on 2-methyl-1-tosyl-2-vinylaziridine. In contrast to the two previous examples, the allylic position of cyclic vinyl aziridines traps the α-diboryl carbanions along the diborylalkylation/ring opening to form exclusively homoallyldiboronate species with *trans* disposition of the amine and diborylalkyl groups. Despite the fact that regioselectivity depends on the nature of vinyl aziridine substrate, the resulting product maintains the two boryl moieties unaltered, except for those reactions where $HCArB_2pin_2$ are involved, since protodeboronation seems to proceed, under the basic reaction conditions, in order to diminish the steric hindrance around the quaternary C centers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript

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